Strahlentherapie
und Onkologie

Dose Escalation in Large Anterior Skull-Base Tumors by Means of IMRT

First Experience with the Novalis® System

Antje Ernst-Stecken[1], Ulrike Lambrecht[1, 2], Reinhold Mueller[1, 2], Oliver Ganslandt[3], Rolf Sauer[1], Gerhard Grabenbauer[1]

Purpose: To evaluate the feasibility and tolerance of dose escalation with stereotactic intensity-modulated radiotherapy (sIMRT) for skull-base tumors.
Patients and Methods: Between 01/2003 and 12/2004, twelve patients were treated. Nine were exclusively treated at the Novalis® site with one planning target volume (PTV) field boost, three were administered boost IMRT treatment (two with each one PTV-shrinking field, one with single PTV) after conventional three-dimensional conformal radiotherapy. This resulted in 23 PTVs with a median volume of 93.63 cm^3 (range, 88.58–125.88 cm^3). Dose calculation was done by the pencil-beam algorithm. Median total doses of 66.6, 77.4, and 63.9 Gy were prescribed for sIMRT alone, sIMRT after 3-D conformal irradiation of the nasopharynx and cervical lymph nodes with 59.4 Gy, and for reirradiation, respectively.
Results: 95% isodose PTV coverage was reached in 86.5% (range, 80–93%). Homogeneity (D_{max}/D_{ref}) was 1.11, 1.09, and 1.08. Median total doses to 50% of chiasm, right and left optic nerve were 16.21, 16.82 and 10.23 Gy. 11/12 patients are locally controlled with a median follow-up of 11 months (range, 3–23 months), one has died of pulmonary embolism after cerebrospinal dissemination of retinal adenocarcinoma.
Conclusion: SIMRT enables dose escalation to tumors located close to critical organs. Inverse planning for micro-multileaf collimator stereotactic irradiation is practicable in the daily routine irradiation program. SIMRT needs special verification and still, the following parameters have to be standardized: IMRT dose specification, dose maxima, length of radiation delivery time.

Key Words: Stereotactic intensity-modulated radiotherapy · Skull-base tumors · Novalis® system

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Intensitätsmodulierte Radio(chemo)therapie von Schädelbasistumoren. Erste Ergebnisse mit dem Novalis®-System

Ziel: Dokumentation von Praktikabilität und Nebenwirkungen der stereotaktischen intensitätsmodulierten Radio(chemo)therapie (sIMRT) bei komplex geformten Schädelbasistumoren in der Nähe von Risikoorganen mit dem stereotaktischen Linearbeschleuniger Novalis® (BrainLAB AG, Heimstetten).
Patienten und Methodik: Von Januar 2003 bis Dezember 2004 wurden zwölf Patienten wie folgt behandelt: neun ausschließlich am Novalis®-System mit je einer Feldverkleinerung, drei im Rahmen einer Boostbestrahlung (davon zwei mit je einer Feldverkleinerung, einer mit nur einem Boostvolumen). Daraus resultierten 23 Zielvolumina mit einer medianen Größe von 93,63 cm^3 (88,58–125,88 cm^3). Die mediane Gesamtdosis betrug für alleinige sIMRT 66,6 Gy, für sIMRT im Anschluss an konventionelle dreidimensionale konformale Radiotherapie wegen eines Nasopharynxkarzinoms 77,4 Gy und 63,9 Gy bei Re-Bestrahlungen.
Ergebnisse: Die 95%-Isodose umfasste median 86,5% (80–93%) der Zielvolumina. Die Homogenität (D_{max}/D_{ref}) betrug median 1,09 (1,08–1,11). Die mediane, 50% des Chiasmas, des rechten und linken Nervus opticus belastende Gesamtdosis lag bei 16,21, 16,82 and 10,23 Gy. 11/12 Patienten sind bei einem medianen Nachbeobachtungszeitraum von 11 Monaten (3–22 Monate) in lokaler Kontrolle, ein Patient mit retinalem Adenokarzinom starb an einer Lungenembolie nach zerebrospinaler Dissemination.
Schlussfolgerung: Die sIMRT erlaubt eine sichere Dosiseskalation bei Tumoren in unmittelbarer Nähe des optischen Apparats. Die inverse Planung für microMLC-Bestrahlung in Step-and-shoot-Technik ist in der täglichen Routine einsetzbar. Sie benötigt eine spezielle Verifikation. Folgende Parameter müssen noch standardisiert werden: IMRT-Dosisspezifikation, erlaubte Höhe und Größe von Dosismaxima, Dauer der Bestrahlungsapplikation.

Schlüsselwörter: Stereotaktische Radiotherapie · Intensitätsmodulierte Radiotherapie · Schädelbasistumoren · Novalis®-System

[1] Department of Radiation Therapy and Novalis Shaped Beam Surgery Center, University Hospital of Erlangen-Nuremberg, Erlangen, Germany,
[2] Division of Medical Physics, Department of Radiation Therapy, University Hospital of Erlangen-Nuremberg, Erlangen, Germany,
[3] Department of Neurosurgery, University of Erlangen-Nuremberg, Erlangen.

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Introduction

With the advent of advanced radiation techniques, highly conformal radiotherapy can be performed. Especially intensity-modulated radiotherapy (IMRT) has shown the potential of dose sparing to organs at risk (OARs) close to complex planning target volumes (PTVs) [4, 9, 11, 15, 22, 28]. A major advantage of IMRT may also result from dose escalation with doses being somewhat between 25% and 30% greater than used with three-dimensional conformal conventional radiotherapy (3D-CRT). As for specific indications, early trials with node-positive lung cancer [10] and tumors located near the skull base [25, 27] have been reported. Another relatively new radiotherapeutic device is the dedicated stereotactic linear accelerator. Fractionated stereotactic radiotherapy appears to yield high precision together with less toxicity. Especially for tumors located near the skull base or in the orbita, this approach may help to preserve or improve vision [24]. In addition, for some tumors near the skull base and optic pathway, i.e., nasopharyngeal cancer, squamous cell carcinomas of the paranasal sinuses, chondromas and chondrosarcomas, evidence for dose-response relationship is well known and a total dose > 66 Gy is clearly necessary to reach sufficiently high local control rates (LCRs) [12]. Another clinical and technical challenge is reirradiation [23].

This paper gives early technical and clinical results of stereotactically guided intensity-modulated therapy (sIMRT) for selected tumors of the anterior skull base.

Patients and Methods

Patient and Treatment Characteristics

Between 01/2003 and 12/2004, a total of twelve patients with tumors located at the anterior skull base and close to the optic pathway were considered eligible for sIMRT for possible dose escalation with the Novalis® system (BrainLAB AG, Heimstetten, Germany). Patient and tumor characteristics are summarized in Table 1.

Treatment Planning and Delivery

All patients were immobilized in a thermoplastic stereotactic head mask (BrainLAB AG, Heimstetten, Germany). Thereafter, helical CT images of 1 mm slice thickness (Somatom VZ, Siemens, Erlangen, Germany) were obtained with the localizer box attached to the mask system and these were fused with the previously generated thin-slice (0.8–1.0 mm) MR images (Magnetom Sonata, Siemens, Erlangen, Germany) by the automatic image fusion system software. Positioning of the patients was performed using the BrainLAB™ target positioner box.

The tumors were planned using the Novalis® Brain Scan Treatment Planning System (Version 5.31, BrainLAB AG, Heimstetten, Germany). The treatment delivery sys-tem consisted of a 6-MeV linear accelerator coupled to a micro-multileaf collimator (mMLC) with 26 pairs of leafs mounted permanently to the linac: from the inner to the outer side of the collimator 14 pairs with 3-mm pitch, six pairs with 4.5-mm pitch, and six pairs with 5.5-mm pitch [5]. SIMRT was performed using a median of six (range, five to eight) conformal, intensity-modulated fields with ten intensity steps each. Per treatment session, a median total number of 730 monitor units (MU) was delivered (range, 583–1,039 MU).

Dose calculation for sIMRT was done by the pencil-beam algorithm. Here, inhomogeneities are taken into account by attenuating the primary photon fluence exponentially utilizing the average total linear attenuation coefficient of intervening tissue, by multiplying photon fluence by linear attenuation coefficient to yield the number of collisions in the scattering volume, and by scaling the path between the scattering volume element and the computation point by an effective tissue. The algorithm is characterized by a fast and accurate dose calculation for large and irregular fields and for IMRT although secondary dose distribution will not be density-corrected and large cavities can still give errors

Table 1. Patient and tumor characteristics. F: female; FU: fluorouracil; M: male; SCC: squamous cell carcinoma.

Tabelle 1. Patienten- und Tumorcharakteristika. F: weiblich; FU: Fluorouracil; M: männlich; SCC: Plattenepithelkarzinom.

Patient #	Age (years)	Gender	Site	Histology	Prior surgery	Chemotherapy	Total dose (Gy)
1	27	F	Frontal skull base	Chondrosarcoma II°	+		70.2
2	66	M	Frontal skull base	Recurrent chondrosarcoma I°	+		68.4
3	37	F	Frontal skull base	Esthesioneuroblastoma	+		68.4
4	65	M	Nasopharynx	Recurrent SCC		Mitomycin	68.4
5	46	M	Nasopharynx	Lymphoepithelial cancer		FU/cis-DDP	79.4
6	46	M	Nasopharynx	Lymphoepithelial cancer		FU/cis-DDP	77.5
7	72	M	Nasopharynx	Lymphoepithelial cancer		FU/cis-DDP	74.8
8	47	M	Orbita	Retinal adenocarcinoma	+		64.0
9	39	F	Paranasal sinus	Adenocarcinoma	+	FU/cis-DDP	66.6
10	61	M	Paranasal sinus	Recurrent SCC	+	Cis-DDP	59.5
11	47	M	Paranasal sinus	Transitional cell carcinoma	+		63.0
12	48	F	Paranasal sinus	Rhabdomyosarcoma		CWS 2002-P	54.0

[18]. For sIMRT dose planning, the guardian was the relative weighting between OARs. The maximum dose for different partial volumes can be defined. For the OARs, i.e., right and left optic nerve and chiasm, additional partial volume constraints were to be defined (Figure 1). All patients received 1.8 Gy per fraction daily, with five fractions per week except the patient with rhabdomyosarcoma who was treated with 1.8 Gy bid. Median total dose was 66.6, 77.4, and 63.9 Gy for patients receiving sIMRT alone, sIMRT boost after 3D-CRT of the primary and neck nodes, and reirradiation, respectively.

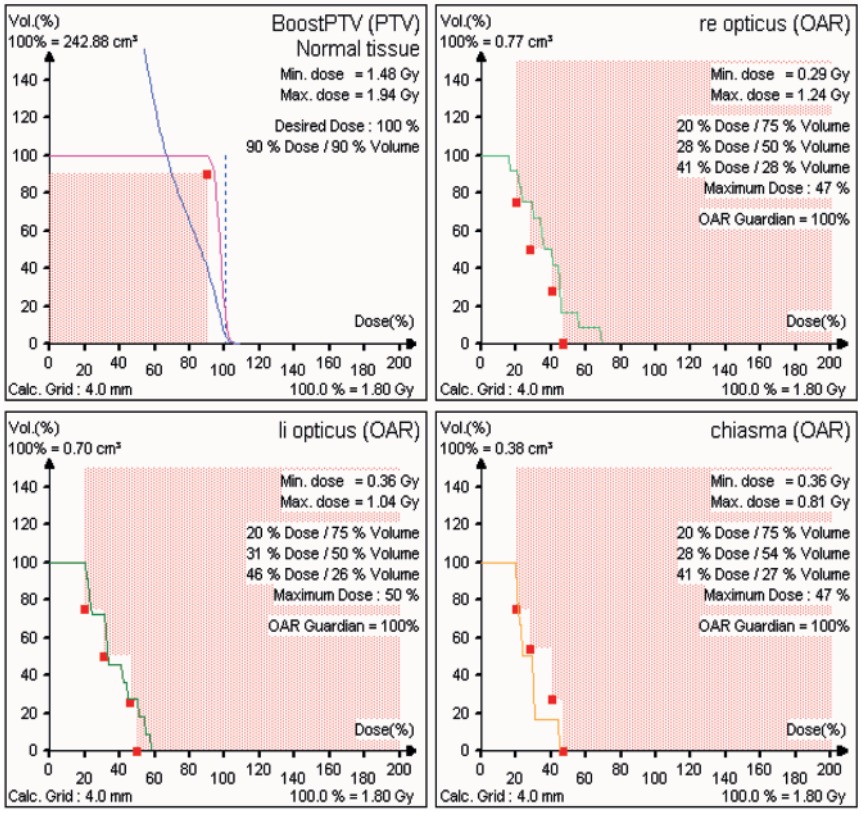


Figure 1. Dose constraints for stereotactic intensity-modulated radiotherapy. Guardian: relative weighting between organs at risk; li opticus: left optic nerve; OAR: organ at risk; re opticus: right optic nerve; PTV: planning target volume.

Abbildung 1. Dosisgrenzen für die stereotaktische intensitätsmodulierte Radiotherapie. Guardian: relative Wichtung der Risikoorgane; li opticus: linker N. opticus; OAR: Risikoorgan; PTV: Planungszielvolumen; re opticus: rechter N. opticus.

Quality Criteria and Evaluation

For IMRT, 90% isodose coverage for 90% of the PTV was required. D_{min} inside PTV and D_{max} were documented. There are different methods for dose verification in IMRT [1, 33]. We use the radiographic film, who permits to measure the dose in a matrix of points [3]. The steep dose gradient is registered on a radiographic film first for the whole plan with all fields in the coronal plane of the IMRT phantom and afterwards for each single field. This procedure is done once before the beginning of treatment. The distribution of the optic density in the film has to be compared to the calculated distribution by using the software OmniPro I'mRT™ (Scanditronix Medical AB, Uppsala, Sweden, 2003).

Follow-up and Statistics

We evaluated the following points: quality of sIMRT using the above-mentioned quality criteria, tumor response after hypofractionated stereotactic radiotherapy (hfSRT) with MRI 8 weeks after the end of hfSRT and every 3 months thereafter. Furthermore, side effects, especially concerning the optic apparatus and deficits of cranial nerves, were documented by obtaining visual acuity and perimetry every 3 months.

Results

Organs at Risk and Clinical Outcome

Left and right optic nerves and chiasm were considered OARs. Given the applied technique, doses as shown in Table 2 were given to these OARs. With a median follow-up of 11 months (range, 3–22 months), no patient experienced side effects concerning a deterioration of vision and visual field. In one patient with N. VI paresis, this resolved 8 months after treatment (see Figures 2a to 2d).

Local Tumor Control and Survival

One patient with adenocarcinoma of the retina experienced tumor recurrence. Here, 3 months after the end of treatment, cerebrospinal dissemination occurred. He was scheduled for craniospinal irradiation and died of pulmonary embolism during radiotherapy. The primary tumor had been treated surgically first with R1 resection at the chiasm and R0 resection 8 weeks after the first surgery. Thereafter, adjuvant local sIMRT was performed due to the lack of cerebrospinal tumor dissemination with MRI and cerebrospinal fluid cytology. All other patients are currently alive and have their tumors controlled.

Case Example of sIMRT Boost after Three-Dimensional Conformal Therapy

This was a 51-year-old man with T4 N2a nasopharyngeal cancer (Figures 2a to 2d). Definitive simultaneous radiochemo-

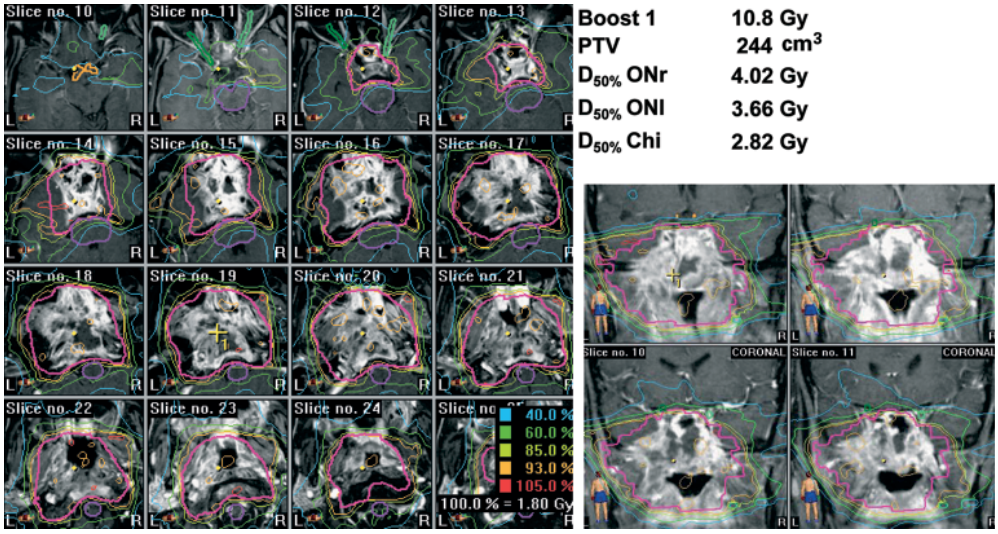


Figure 2a – Abbildung 2a

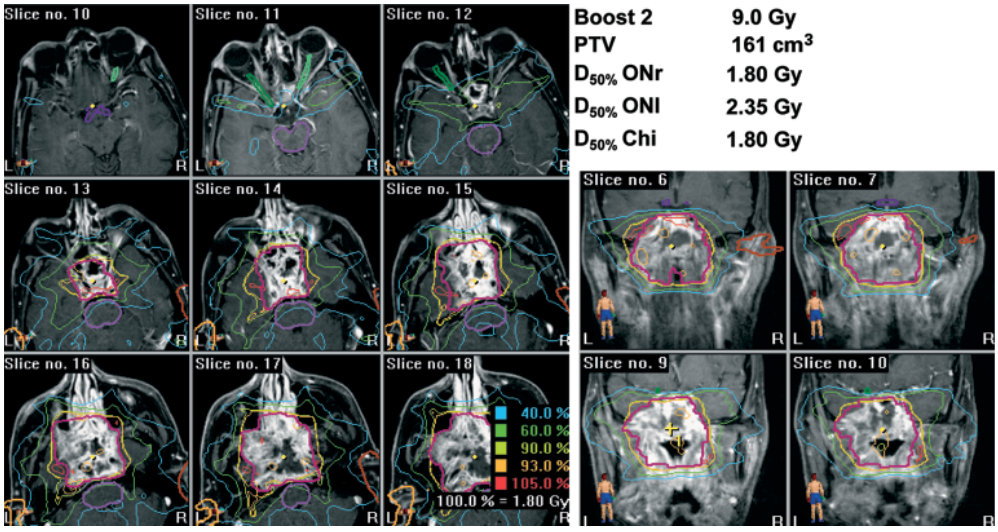
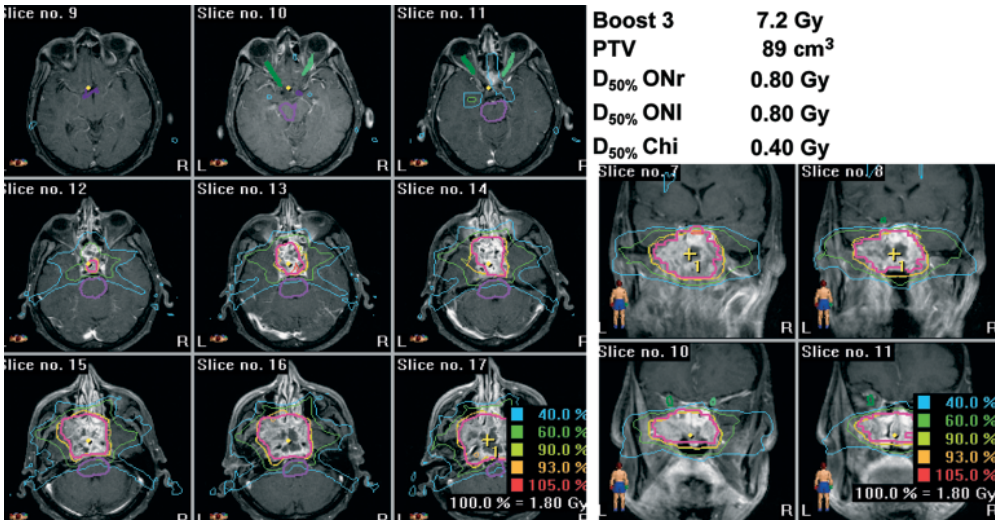


Figure 2b – Abbildung 2b



Figures 2a to 2d. Nasopharyngeal cancer, primary radiochemotherapy. a) First boost after conventional three-dimensional conformal irradiation of primary and neck nodes with 50.4 Gy. b) Second boost. c) Third boost.
(continued on page 187)

Abbildungen 2a bis 2d. Nasopharynxkarzinom, primäre Radiochemotherapie. a) Erster Boost nach 50,4 Gy (konventionelle dreidimensionale konformale Radiotherapie von Primärtumor und Lymphabfluss). b) Zweiter Boost. c) Dritter Boost.
(Fortsetzung auf Seite 187)

Figure 2c – Abbildung 2c

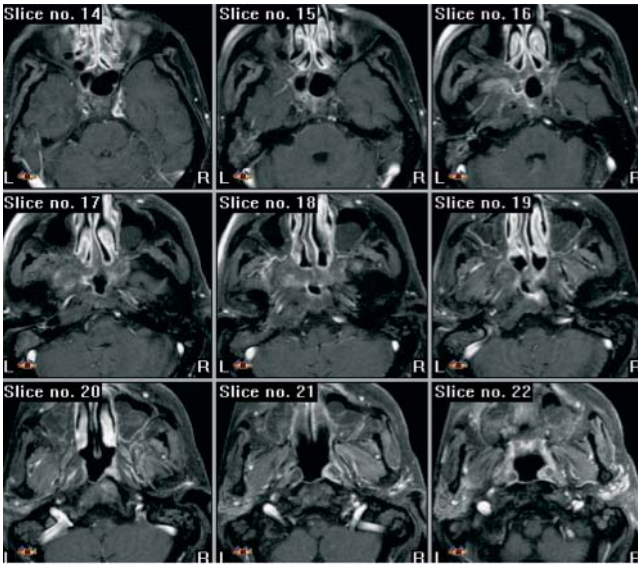


Figure 2d – Abbildung 2d

Figures 2a to 2d. Nasopharyngeal cancer, primary radiochemotherapy. d) Follow-up after 18 months, complete remission.

Abbildungen 2a bis 2d. Nasopharynxkarzinom, primäre Radiochemotherapie. d) Nachuntersuchung nach 18 Monaten, komplette Remission.

therapy with 5-fluorouracil (5-FU) and cis-DDP was performed. Primary tumors including the neck nodes were irradiated with 50.4 Gy by conventional 3D-CRT. Thereafter, dose escalation to the primary with a total dose of 77.4 Gy by sIMRT was performed. Doses to OARs ($D_{50\%}$) were 57 Gy and 55 Gy for the right/left optic nerve and the chiasm, respectively.

Quality Criteria

Given the above-mentioned technique, PTV coverage and doses as listed in Table 3 could be reached. Homogeneity was good within RTOG guidelines, whereas coverage was moderate with a median of 80% of the PTVs covered by 95% of the prescription dose.

Discussion

Dose Escalation

Recently published data has shown significantly higher LCRs for dose escalation for tumors located near the skull base. For nasopharyngeal cancer, doses > 66 Gy, delivered in IMRT technique, revealed significantly higher LCRs [12]. Conventional external radiotherapy with a dose of around 60 Gy is inadequate in the treatment of clival chordomas [34] and chondrosarcomas [21, 27]. For these highly diffentiated tumors, due to the attractive dose profile of protons and the increased biological effectivity of heavy ions, the latter particles were favored for first-line therapy [6, 20, 26, 27, 29]. Nevertheless, the required facilities are still rare and treatment remains expensive. For a small number of patients with limited mobility or refusal of consent in proton or particle therapy, as it was given in our two patients with chordoma and chondrosarcoma, sIMRT might be an effective alternative. Paranasal sinus cancer is a very rare disease where 70 Gy for definitive treatment is needed to achieve acceptable LCRs. A significant prognostic parameter for worse LCR is invasion through the cribriform plate [7], so that especially in these patients dose escalation in the bony skull-base structures near the critical organs (optic nerve and chiasm) is preferred. With IMRT, dose escalation and a favorable toxicity profile can be achieved which is underlined by other as well as our data [12].

Altered Fractionation Schemes

Especially in head and neck cancer, good clinical evidence exists for improved tumor control rates and survival by accelerated fractionation schedules [13, 17]. These altered fractionation schemes seem to yield higher LCRs also in case of parameningeal rhabdomyosarcoma [16]. On the other hand, with 2-D-planned radiotherapy, accelerated-hyperfractionated radiotherapy is known to be associated with significantly increased radiation-induced damage to the central nervous

Table 2. Total doses to organs at risk [median (range)]. D_{min}: minimum dose; $D_{50\%}$: dose to 50% of volume; D_{max}: maximum dose.

Tabelle 2. Risikoorgandosen. D_{min}: Dosisminimum; $D_{50\%}$: Dosis auf 50% des Volumens; D_{max}: Dosismaximum.

Dose (Gy)	Chiasm	Right optic nerve	Left optic nerve
D_{min}	4.11 (0.50–30.70)	6.51 (0–41.75)	2.82 (0–37.62)
$D_{50\%}$	16.21 (1.20–44.01)	16.82 (0–49.08)	10.23 (0–40.27)
D_{max}	38.28 (1.30–68.44)	36.63 (0–62.50)	38.51 (0–58.24)

Table 3. Quality of stereotactic intensity-modulated radiotherapy (sIMRT). PTV: planning target volume.

Tabelle 3. Qualität der stereotaktischen intensitätsmodulierten Radiotherapie (sIMRT). PTV: Planungszielvolumen.

Number PTVs	12	10	1
Median volume (cm^3)	125.88	66.41	88.58
Median PTV coverage by 95% isodose	80%	80%	93%
D_{ref}	1.8 (1.6 one patient)	1.8 (1.6 one patient)	1.8
D_{min}	1.33	1.33	1.55
D_{max}	2.0	1.97	1.94
D_{max}/D_{ref} (homogeneity)	1.11	1.09	1.08

system, including temporal lobe, cranial nerves, optic nerve and chiasm, brainstem, and spinal cord. This was recently shown in a study by Teo et al. in 2000 [30]. Given these severe limitations of accelerated treatment in skull-base tumors, an urgent need for IMRT in these tumors is evident. In our patient collective, one with rhabdomyosarcoma was treated with 1.6 Gy bid according to the CWS 2002-P treatment protocol. The tumor was located in the ethmoidal sinus with an infiltration of the skull base and growth along the frontal sinus on both sides. Consequently, a T-formed tumor shape resulted. With sIMRT, right and left optic nerve and chiasm received a mean fractional dose of 0.37, 0.42, and 0.32 Gy, respectively, while treating the PTV to a total dose of 54 Gy. Thus, for selected case, calling for accelerated treatment, this approach would appear safer with advanced techniques that guarantee very low doses to OARs.

Imaging for Treatment Planning and Quality Criteria of IMRT

Although there is a widespread availability of modern imaging devices including magnetic resonance scanners which appear the preferable imaging modality for tumors located along the skull base, there are numerous recent treatment-planning studies on advanced techniques based on 3-mm slice CT images [2, 14, 15, 31]. Given the two possibilities, on the one hand to shape the dose distribution very close, i.e., within a range of a few millimeters around the PTV and OAR and, on the other hand, ensure a very rigid fixation of the patient head, we recommend to use 0.4- to 1.0-mm MR images that are fused to 1-mm CT planning scan, whenever possible.

IMRT always creates a rather inhomogeneous dose distribution throughout the PTV which might be unfavorable in terms of local control. In contrast to conventional 3D-CRT, where the recommendations of ICRU 50 report are well accepted, for IMRT, no recommendations for dose prescription, coverage, homogeneity, maxima, length of delivery time, and verification have been made yet. Our data (Table 3) show a relatively moderate median coverage of 80% of the PTVs by the 95% isodose, which we considered to be acceptable with a good homogeneity inside the target at the same time. Consequently, IMRT still has to prove as high long-term LCRs as conventional radiotherapy, because follow-up times are still short. In addition, tumor control may be adversely affected by the lower radiation dose rate which is associated with the delivery technique. The Novalis® system works with the step-and-shoot technique. Using ten intensity steps per field and given a number of five to eight fields, a delivery time of nearly 20 min results for the application of 1.8 Gy per fraction. Recent radiobiological data suggest that any radiotherapy schedule that requires more than 0.5 h for the delivery of 1.8–2.0 Gy should be regarded as truly experimental due to a possible decrease of biological effect following the lower dose rate [8, 19, 28, 32]. It has been suggested to compensate the lower dose rate by an increase in total dose of about 10%, although clinical data lack until now.

Conclusion

Our data show that sIMRT is a safe and effective tool for the treatment of complex-shaped tumors near the optic pathways to achieve better dose escalation as single therapy or in combination with conventional 3D-CRT. Quality criteria for dose prescription and delivery times still have to be defined as well as long-term tumor control is to be proven.

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Address for Correspondence
Dr. Antje Ernst-Stecken
Strahlentherapeutische Universitätsklinik
Universitätsstraße 27
91054 Erlangen
Germany
Phone (+49/9131) 85-3405, Fax -9335
e-mail: antje.ernst-stecken@strahlen.imed.uni-erlangen.de