Clinical results of intensity-modulated radiation therapy (IMRT) for tumors of the head and neck region*

Minireview

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Intensity-modulated radiation therapy (IMRT) is an advanced form of the three-dimensional conformal radiation therapy (3D-CRT). Highly conformal dose distribution is the basic feature of IMRT. The head and neck region is suitable for this new technology since the primary tumor is often surrounded by several critical structures. IMRT offers the ability of dose escalation due to steep dose gradient towards healthy tissues. In this review, clinical results of IMRT in several head and neck sites are presented, including intracranial tumors. Parotid-sparing strategies and patterns of local-regional failures are analyzed. The possibilities of irradiation of recurrent malignancies are mentioned. In perspective, the potential of IMRT should be explored in conjunction with altered fractionation regimens, including simultaneous integrated boost (SIB). Particularly, studies with dose escalation are desirable.

Key words: IMRT, intracranial tumors, head and neck cancer, patterns of failure

Intensity-modulated radiation therapy (IMRT) is an advanced method of the delivery of radiation through the beams with non-uniform radiation fluence [57]. Contrary to the three-dimensional conformal radiation therapy (3D-CRT), IMRT is able to combine both spatial beam shaping and fluence modulation across the beam (Fig. 1 and 2). As a result, highly conformal dose distribution can be achieved that allows improved sparing of healthy tissues. It holds true for the target volumes of complex and even concave shape. The planning studies comparing IMRT with conventional radiotherapy or 3D-CRT confirmed the dosimetric advantages of this novel method for many tumor sites [4, 26, 37, 43].

The region of head and neck is suitable for the application of IMRT for several reasons. First, the anatomy is very complex with many dose-limiting structures. Tolerance doses for partial volumes (expressed as the probability of 5 % complication within five years from treatment – TD 5/5) of the most important normal tissues in the head and neck region are as follows: brain 60 Gy, brainstem 60 Gy, eye lens 10 Gy (no partial volume), retina 45 Gy (no partial volume), optic nerves and chiasma 50 Gy (no partial volume), spinal cord 50 Gy (5 cm), and parotid gland 32 Gy [13]. By contrast, radiation doses able to control the majority of head and neck malignancies lie in the range of 60 Gy to more than 70 Gy. Second, physiological organ movement is minimal and rather advanced methods of immobilization are available. The thermoplastic head mask combined with the head and neck cast is considered appropriate. Using such device, the standard deviation of systematic and random set-up errors can be less than 2.0 mm [27]. Third, dose escalation is feasible using IMRT without exceeding the tolerance doses for normal tissues. This is extremely important, as many tumors in the head and neck region, especially squamous cell carcinomas, showed a clear dose-response relationship [17, 23].

The aim of this article is to summarize contemporary clinical experience with IMRT in the treatment of intracranial tumors and head and neck tumors.

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Figure 1. Fluence pattern of the IMRT field.

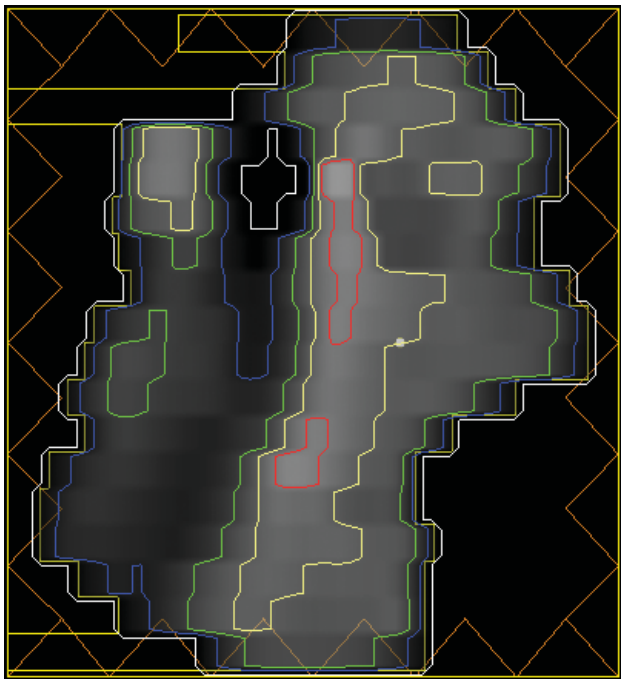

Figure 2. Fluence pattern of the IMRT field including dose isolevels.

Intracranial tumors

High-grade glioma. Two groups explored hypofractionated IMRT regimens in the primary treatment of glioblastoma multiforme (GBM) (Tab. 1). SULTANEM et al from the McGill University, Montreal irradiated 25 patients using forward-planning intensity modulation [51]. A total dose of 60 Gy in 20 fractions over 4 weeks was delivered to the gross tumor volume (GTV) represented by the contrast-enhancing lesion on the postoperative MRI scans. Among inclusion criteria, the maximal postoperative tumor volume of 110 cm^3 or less was allowed. The planning target volume (PTV) that covered a margin of 15 mm received 40 Gy in 20 fractions. At a median follow-up of 8.8 months, no radiation-induced late toxicity occurred and 4 of 25 patients were alive without graphic evidence of tumor progression. Only local failures were observed with no recurrences occurring farther in the brain.

A pilot study was performed at the Baylor College of Medicine, Houston using the NOMOS Peacock system [14]. Before intervention, the primary tumor should not exceed 6 cm in greatest diameter. The enhancing tumor or surgical cavity received a dose of 50 Gy in 10 fractions over 2 weeks, whereas the surrounding edema was treated to 30 Gy in 10 fractions. Of the 18 evaluated patients, three experienced radiation necrosis requiring surgical intervention. Histopathologic evaluation of resection specimens confirmed radiation necrosis in all cases. No recurrence was recorded beyond 2 cm from the primary lesion.

The efficacy of irradiation in high-grade gliomas is limited by the inherent radioresistance of glioma cells and the radiosensitivity of the surrounding brain tissue [36]. Focal dose escalation beyond 60 Gy is feasible using advanced technologies, but the predominant failure pattern remains local [3, 49]. In selected patients, the external beam radiotherapy followed by stereotactic radiosurgery or interstitial brachytherapy yielded a survival benefit of about 6 months [21, 49]. The median survival times reported in the two IMRT studies did not differ from conventional treatment series. Relatively good tolerance was apparent when large doses per fraction were delivered to the GTV or resection cavity. The rate of radiation necrosis – 3 of 18 patients in the Floyd's study – is less than anticipated if relatively large dose per fraction (5 Gy) is taken into account. Nevertheless, treatment-induced necrosis seems to be necessary to control this aggressive disease.

Definitive conclusions regarding hypofractionated IMRT for malignant gliomas cannot be drawn due to small numbers of patients. Looking at the patterns of recurrence, the high-dose region should include not only the GTV or resection

Table 1. IMRT for glioblastoma multiforme

	Patients	Total dose (Gy)	Regimen	Late toxicity Grade ≥3*	Median survival (months)
Montreal [51]	n=25	60	20x3 Gy	0/25	9.5
Houston [14]	n=18	50	10x5 Gy	3/18	7.0

*Radiation Therapy Oncology Group neurotoxicity scores

cavity but also a margin of about 5–15 mm. Perhaps better local control could be achieved at the expense of grater incidence of radiation necrosis. Of course, only selected patients with smaller tumors will be suitable for such treatment strategy. Given the natural aggressiveness of GBM, it is unrealistic to expect a significant benefit from IMRT for the whole patient population.

VOYNOV et al. from the University of Connecticut Health Center, Farmington treated 10 patients with recurrent high-grade gliomas using stereotactic directed IMRT [56]. Tumor histologies at the time of relaps included GBM in 5 patients and anaplastic astrocytoma (AA) in another 5 cases. Partial resection before IMRT was performed in five patients. A dose of 30 Gy was delivered in six daily fractions of 5 Gy. The median survival time was 10.1 months and 3 patients survived two years.

Low tumor burden (median volume 35 cm^3) and a 50 % proportion of patients with AA probably contributed to quite a long median survival. Comparable results were achieved in selected patients with recurrent GBM using stereotactic radiosurgery or interstitial brachytherapy [50]. An apparent advantage of IMRT in comparison with the two aforementioned methods consists in the ability of covering irregularly shaped tumor volumes.

Meningioma. IMRT with the NOMOS Peacock system was used for the treatment of 40 patients with intracranial meningioma at the Methodist Hospital and Baylor College of Medicine, Houston [54]. Postoperative radiotherapy was performed in 25 patients while the remaining 15 patients were primarily treated with irradiation. Tumor or tumor bed with a margin of 5 to 10 mm represented the PTV. The median prescribed dose was 50.4 Gy in daily fractions of 1.71 to 2 Gy. The mean dose delivered to the target ranged from 44 to 60 Gy (median 53 Gy). Late neurotoxicity Grade 3 or higher according to the Radiation Therapy Oncology Group (RTOG) criteria was observed in two patients. One patient had biopsy-proven radiation necrosis at the pontomedullary junction (mean dose 54.1 Gy). The other patient experienced personality changes and memory loss. Repeated MRI revealed edema around the target volume responding to steroids.

PIRZKALL et al from the German Cancer Research Center, Heidelberg reported on 20 patients with skull-base meningiomas that were treated using IMRT with the step-and-shoot technique [47]. Sixteen patients received postoperative irradiation, either for subtotal resection or recurrence. Primary radiation therapy was performed in four patients with convincing clinical symptoms and radiographic findings. PTV was defined as an area of contrast enhancement on MRI plus 1 to 2 mm margin. The median target volume was 108 cm^3 (range, 27–278 cm^3). A dose of 57.6 Gy was prescribed to the isocenter in daily fractions of 1.8 Gy. The mean PTV dose ranged from 55.8 to 58.2 Gy. Late eye toxicity developed in one patient but it could not be clearly distinguished from the optic neuropathy relating to the meningioma infiltration. After a minimum follow-up of 18 months, not a single patient showed progression on MRI examinations.

GRANT et al successfully treated the optic sheath meningioma using IMRT with a dose of 50 Gy in 25 fractions [19]. The patient experienced complete recovery of her perimeter and was stable 3 years after radiotherapy.

For benign meningiomas, the risk of recurrence is substantially greater if the total resection cannot be accomplished. LUK et al reported the 5-year survival rate of 88 % after complete resection in comparison with 48 % after incomplete surgery [34]. TAYLOR et al analyzed the treatment results in a group of 132 patients with intracranial meningiomas [53]. The actuarial 10-year local control rates for total resection, subtotal resection, and subtotal resection plus adjuvant radiotherapy were 77 %, 18 %, and 82 %, respectively. The corresponding 10-year overall survival rates were 93 %, 81 %, and 49 %, respectively. Local control achieved in the two IMRT trials compares favorably with conventional radiotherapy series, although the median follow-up is still short (Tab. 2).

Meningiomas at certain sites of the skull base, such as cerebellopontine angle, clivus, or the anterior part of the foramen magnum, are less readily accessible for the surgery. As a result of that, a substantial proportion of patients are affected by severe morbidity. COULDWELL et al analyzed a group of 109 patients operated on in three hospitals for petroclival meningiomas [10]. Permanent cranial nerve deficits were observed in 36 patients (33 %), especially in association with the cavernous sinus involvement. In such tumor locations, it seems reasonable to combine a subtotal resection with IMRT or to use IMRT alone. Doses generally recommended for the treatment of benign meningiomas lie in the range of 50 to 54 Gy. A retrospective analysis of GOLDSMITH et al suggested a dependency of local control on total dose [18]. The 10-year progression-free survival in a group of 117 patients was significantly longer when a fractionated dose higher than 52 Gy was delivered (p=0.04). In order to achieve optimal local control, doses of 54–60 Gy to the tumor are desirable while keeping the dose to critical structures (optic nerves, optic chiasma, retina, cranial nerves, brainstem) below 50 Gy. This is the main reason why IMRT should be utilized in benign meningiomas.

Table 2. IMRT for benign meningioma

	Patients	Mean dose (Gy)	Median targer volume (cm^3)	Late toxicity Grade ≥3*	Local control (%)
Houston [54]	n=40	44–60	20.2	2/40	93 5-year
Heidelberg [47]	n=20	55.8–58.2	108	0/20	100 18 months**

*Radiation Therapy Oncology Group neurotoxicity scores, **minimum follow-up.

Medulloblastoma. Twenty-six children treated for medulloblastoma at the Methodist Hospital and/or Texas Children's Hospital, Baylor College of Medicine, Houston were retrospectively studied [24]. All patients received both radiotherapy and chemotherapy. Craniospinal irradiation was followed by conventional posterior fossa boost (n=11) or a boost delivered by IMRT (n=15). The total dose to posterior fossa in children with conventional and IMRT boost was 54 Gy and 55.8 Gy, respectively. The auditory apparatus received the mean doses of 54.2 Gy and 36.7 Gy, respectively. On audiometric evaluation, 64 % of patients suffered from Grade 3–4 hearing loss in the group with conventional boost compared to 13 % in the IMRT group ($p<0.01$).

Radiation-induced hearing loss occurs in up to 50 % of patients after temporal bone irradiation with doses of 50–60 Gy [1]. In a number of tumor sites, it is necessary to include the auditory apparatus into the PTV – brain tumors affecting the temporal lobe, posterior fossa tumors, nasopharyngeal carcinoma, and parotid gland carcinoma. Moreover, chemotherapy-induced hearing loss associated with regimens containing platinum agents is well documented [16]. SCHELL et al observed a high probability of hearing loss in irradiated children and young adults who later received cisplatin, although the cumulative dose was as low as 270 mg/m^2 [48]. As it was shown in the HUANG's work, IMRT can offer substantial sparing of the auditory apparatus. On the other hand, coverage of the target volume near the inner and middle ear (region of cerebellar peduncles) seems to be rather compromised. Further studies with larger patient numbers will be needed to confirm these early results.

Head and neck tumors

Nasopharyngeal carcinoma. An update of the University of California-San Francisco (UCSF) experience with IMRT in nasopharyngeal carcinoma included 67 patients who were treated using three different methods of delivery of non-uniform radiation beams [31]. The GTV and positive neck nodes received a dose of 65–70 Gy. In selected patients, external beam radiotherapy was followed by high-dose-rate (HDR) brachytherapy (n=26) or gamma knife (n=1) boost. The intracavitary brachytherapy boost consisted of 5–7 Gy in two fractions. The 4-year actuarial local control, local-regional control, and overall survival rates were 97 %, 98 %, and 88 %, respectively. Distant metastases developed in 17 of 67 patients (25 %), all of them having Stage III or IV disease. Severe late toxicity Grade 3–4 according to RTOG scale developed in 8 of 67 patients (12 %), hearing loss being the most frequent (n=5). All patients with Grade 4 hearing loss had also chemotherapy. Xerostomia appeared to decrease with time after irradiation. Thirteen of the 41 evaluable patients suffered from Grade 1 xerostomia and only one patient had Grade 2 symptoms after two years from IMRT.

Local failure rates following radiation therapy for American Joint Committee on Cancer (AJCC) 1992 Stage T1 and T2 nasopharyngeal tumors ranged from 6 % to 32 %. Substantially higher recurrence rates were reported for T3 and T4 disease, ranging from 32 % to 88 % [22, 46]. Addition of chemotherapy to radiotherapy was shown to improve the results of treatment in locally advanced disease. HUNCHAREK et al performed a meta-analysis of all available randomized trials that compared chemoradiation with radiotherapy alone [25]. Two- and 4-year overall survival was increased by 20 % and 21 % for those receiving chemoradiation.

The results achieved at the UCSF using IMRT look quite impressive since 29 of 67 patients (43 %) had primary tumors Stage T3–4. It is difficult to assess the contribution of particular treatment modalities as 39 % of patients had the brachytherapy boost and as much as 75 % of patients also received concomitant and adjuvant chemotherapy. Nevertheless, two important advantages are unquestionably associated with the IMRT method: better coverage of the target volume and a higher dose per fraction (2.12–2.25 Gy) delivered to the GTV. It has been demonstrated that the local control rate in nasopharyngeal carcinoma was dose-dependent [55]. At the Daniel den Hoed Cancer Center, University Hospital Rotterdam, forty-two patients with HDR brachytherapy boost were compared with the control group of patients who did not receive brachytherapy [32]. The 3-year local control rate was 86 % and 60 % for the brachytherapy and external-beam radiotherapy groups, respectively ($p=0.004$). The combined treatment was most beneficial for patients with T1–3 tumors.

As stated above, IMRT provides superior dose distribution in comparison with conventional radiotherapy. HUNT et al described inadequate coverage of the target volume using conventional treatment [26]. The prescribed dose to gross primary disease and positive neck nodes was 70 Gy. The mean PTV doses were 67.9 Gy and 74.6 Gy for the conventional and IMRT plans, respectively. As low as 46 % of the PTV received 70 Gy or more with the conventional plan compared to 87 % with 3D-CRT and 95 % with IMRT. In particular, retropharynx, skull base and medial parts of the neck nodal volumes were underdosed. Both spinal cord and brainstem doses substantially decreased with the IMRT technique. Adequate coverage of the target volume that can be achieved with IMRT undoubtedly contributed to the excellent local control in recently reported series (Tab. 3).

Oropharyngeal and oral cavity carcinoma. Inverse planning IMRT (NOMOS Peacock) was used to treat 12 patients primarily and 14 patients postoperatively at the Washington University Medical Center, St. Louis [5]. According to the 1997 AJCC staging classification, Stage III and IV oropharyngeal carcinoma was present in 11 of 12 definitively treated patients and in 12 of 14 postoperatively treated patients. The median prescribed dose for the primary and postoperatively IMRT was 70.3 Gy and 63.6 Gy, respectively. The 2-year local-regional control was 88 % for the definitive IMRT and 100 % for the postoperative group of patients. Five of the 22 evaluable patients had Grade 2 late xerostomia.

Table 3. IMRT for nasopharyngeal carcinoma

	Patients	Stage III–IV (%)	Dose (Gy)	Late toxicity Grade ≥3*	Local control (%)
San Francisco [31]	n=67	70	65–70**	8/67	97 4-year
St. Louis [7]	n=12	>65	70	NS***	92 2-year

*Radiation Therapy Oncology Group toxicity scores, **IMRT dose excluding brachytherapy, ***not stated

Table 4. Definitive IMRT for oropharyngeal carcinoma

	Patients	Stage III–IV (%)	Dose (Gy)	Late toxicity Grade ≥3*	Local control (%)
Ghent [9]	n=5	100	60–70	NS**	80 1–13 months***
St. Louis [6]	n=31	71	70	0	78 4-year
Ann Arbor [11]	n=43	>80	66–76	NS**	94 3-year

*Radiation Therapy Oncology Group toxicity scores, **not stated, ***follow-up

In an update of this study, CHAO et al showed the importance of tumor volume on the outcome in 74 patients with oropharyngeal carcinoma [6]. Forty-three patients were irradiated postoperatively and 31 patients were primarily treated with IMRT. Platinum-based chemotherapy was given to 17 definitively treated patients. The mean dose for definitive and postoperative radiotherapy was 70 Gy and 66.3 Gy, respectively. The 4-year estimate of local-regional control and disease-free survival was 95 % and 92 % in the postoperative group, and 78 % and 66 % in the definitive IMRT group, respectively. In the 31 patients treated primarily, the GTV and the nodal GTV were measured. In a multivariate analysis, both GTV and nodal GTV were significant independent predictors of local-regional control and disease-free survival.

Fifteen patients with oral cavity carcinoma were included in the analysis of failures following IMRT for head and neck cancer that was published by the same group of investigators from the Washington University Medical Center [7]. Two patients were treated primarily with IMRT and 13 patients received postoperative irradiation. Local-regional failure developed in 5 of 15 patients (33 %).

Local-regional recurrences were analyzed in patients who underwent parotid-sparing IMRT at the University of Michigan, Ann Arbor [11]. Of the 133 patients, 80 had oropharyngeal and 27 had oral cavity carcinoma. A dose of 70 Gy was prescribed to the gross disease, 60–64 Gy to the postoperative bed, and 50–54 Gy to the electively treated neck, at 1.8–2.0 Gy fractions. The proportion of patients with oropharyngeal cancer who received primary and postoperative radiotherapy was approximately equal (43 and 37 patients, respectively). In the oral cavity cancer group, 25 of 27 patients were given postoperative irradiation. The 3-year local-regional control in patients with oropharyngeal tumors (93 %) was significantly better than in patients with oral cavity cancer (59 %). Late toxicity was not reported since the primary goal of the analysis was local failure.

Surgery and radiotherapy are equally effective in the treatment of early oropharyngeal carcinoma (T1–2). For more advanced but operable tumors, surgery and postoperative radiotherapy is a commonly used strategy. Not only disease stage but also a subsite of oropharyngeal cancer is important for the appropriate treatment choice. The rates of local-regional control achieved with definitive IMRT are promising (Tab. 4). Retrospective series of conventional radiotherapy alone showed local control rates ranging from 56 % to 76 % for tonsillar carcinoma and from 44 % to 76 % for base of tongue carcinoma, respectively [28, 35, 39, 45].

It is reasonable to expect better functional outcome following primary IMRT in comparison with combined approach. In the PARSONS' analysis of 6400 patients with oropharyngeal cancer, as much as 20 % of patients with tonsillar carcinoma required segmental mandibulectomy [44]. Among patients with base of tongue carcinoma, 15–20 % required total laryngectomy, 15–20 % underwent mandibulectomy, and 10–25 % required permanent gastrostomy, tracheostomy, or both.

The numbers of patients treated with IMRT for oral cavity carcinoma are quite low in published series [7, 11]. Nevertheless, they recurred more often than those with oropharyngeal carcinoma. To our knowledge, no detailed analysis has been published regarding IMRT for this tumor site.

Other head and neck sites. The segmental IMRT technique was used for the treatment of 48 patients with cancer of the head and neck region at the German Cancer Research Center in Heidelberg [42]. 75 % of patients were irradiated postoperatively. The following tumor sites were comprised: nasopharynx (n=8), oropharynx (n=9), larynx/hypopharynx (n=2), maxillary sinus (n=9), salivary glands (n=18), and unknown primary (n=2). The inclusion criteria for the IMRT treatment were as follows: better sparing of the organs at risk with IMRT compared to 3D-CRT and/or unsatisfactory dose distribution on the 3D-CRT treatment plans. A total dose of 55–72 Gy was prescribed to the PTV in daily fractions of 1.6–2.0 Gy with the exception of 27 patients where daily fraction sizes of 2.0–2.6 Gy were used as an integrated boost. The 2-year actuarial local control and overall survival rates were 93 % and 92 %, respectively. Severe late radiation toxicity according to RTOG criteria occurred in one patient with Grade 4 osteoradionecrosis of the mandible. In respect of

xerostomia, 14 patients suffered from Grade 1–2 symptoms and only one patient had Grade 3 symptoms.

In the frame of the aforementioned trial, investigators from the University of Michigan used parotid-sparing IMRT also for patients with hypopharyngeal (n=12) and laryngeal carcinoma (n=11) [11]. Definitive radiotherapy was performed in 8 of 12 patients with primary tumor in hypopharynx and in 7 of 11 patients with carcinoma of the larynx. The 3-year local-regional control rates for the hypopharyngeal and laryngeal carcinomas were 75 % and 60 %, respectively.

KUPPERSMITH et al from the Baylor College of Medicine reported on the advantages of IMRT in three patients with extensive or recurrent juvenile angiofibroma [29]. The target volume received doses ranging from 34 Gy to 45 Gy. Two children had no signs of disease at 15 and 40 months after treatment. Late toxicity was limited to persistent rhinitis in one patient. Interestingly, the one patient who failed was treated with the lowest dose of 35 Gy. The authors conclude that a radiation dose of 30–35 Gy may not provide the most optimal tumor control.

Salivary gland sparing. EISBRUCH et al analyzed the relationship between the dose distribution in parotid glands and the rate of xerostomia in 88 patients with head and neck cancer [12]. All patients were irradiated using parotid-sparing conformal and segmental IMRT techniques. Saliva was collected from each parotid gland using the suction cup before radiotherapy and regularly up to 12 months thereafter. Stimulated saliva excretion was also measured after a 2-minute exposure to 2 % citric acid solution. A mean dose threshold was defined as 26 Gy for stimulated and 24 Gy for unstimulated saliva flow rates. If the mean dose received by the parotid glands was below or equal this threshold, the salivary output preservation is highly presumable. On the contrary, exceeding the threshold results in very low probability of function maintenance with no recovery over time. The quantitative pertechnetate scintigraphy was used for the evaluation of salivary gland function in 18 patients treated with IMRT at the German Cancer Research Center in Heidelberg [41]. Nasopharyngeal and oropharyngeal primary tumor sites constituted 11 of the 18 patients. At least one parotid gland was irradiated to less or equal 26 Gy in 16 patients. The maximal uptake after treatment was significant for the parotid gland with a dose threshold of 30 Gy. At a median follow-up of 23 months, late xerostomia Grade 1 and 2 was observed in 11 and 3 patients, respectively.

Xerostomia is one of the most bothersome late complications following radiotherapy for head and neck cancer. It has a significant impact on quality of life as it compromises speech and taste. Moreover, the mouth dryness creates a suitable environment for the development of infection, fissures, ulcers, and dental caries. Salivary glands are highly sensitive to irradiation and a dose-response relationship was demonstrated. While substantial recovery of salivary secretion can be expected for the dose range of 40 Gy to 50 Gy, doses above 60 Gy lead inevitably to the irreversible dryness in the majority of patients [15]. Parotid-sparing IMRT is especially feasible at the lower-risk side of the neck. On the contrary, it is limited or even impossible when the ipsilateral nodes, situated medially from the gland (level II and retropharyngeal nodes), are involved or at high risk of microscopic involvement.

Patterns of failure. CHAO et al from the Washington University Medical School analyzed the patterns of recurrence in 126 patients treated with IMRT either definitively (n=52) or postoperatively (n=74) [7]. Concomitant chemotherapy was administered in 67 % of definitively treated patients. Oropharyngeal primary tumor was present in 50 % of patients. The clinical target volume (CTV) 1 covered the primary tumor (surgical bed) and metastatic neck nodes. The CTV2 included the electively treated neck. The mean dose to CTV1 and CTV2 in primarily treated patients was 72.6 Gy (dose per fraction 2.0 Gy) and 64.3 Gy (dose per fraction 1.7 Gy), respectively. The corresponding doses for the postoperatively treated patients were 68.5 Gy (dose per fraction 2.0 Gy) and 61.0 Gy (dose per fraction 1.6 Gy). The mean parotid dose was 17.7 Gy. Nine of 17 failures (53 %) were inside CTV1. The dose-volume histogram analysis showed that the areas of recurrent disease inside CTV were not underdosed in comparison with the rest of CTV. Only one marginal failure was recorded next to the spared parotid gland at the level II lymph nodes.

Remarkably low incidence of local-regional recurrences was reported by the UCSF group [30]. Nasopharynx was the predominant primary site accounting for 86 of 150 cases (57 %). Definitive IMRT was performed in 107 patients (92 had also concurrent chemotherapy), whereas 43 patients were irradiated postoperatively. In patients with definitive IMRT, the mean doses to the GTV and CTV were 74 Gy and 69 Gy, respectively. For the postoperative group, the mean doses of 71 Gy and 66 Gy were delivered to the GTV and CTV, respectively. The mean parotid dose was 29 Gy. Nine of 11 treatment failures occurred at the primary tumor site (paranasal sinuses 6, nasopharynx 2, tonsil 1).

EISBRUCH et al recently reported a detailed analysis of local recurrences following parotid-sparing IMRT [11]. Sixty patients were primarily irradiated with IMRT and 73 patients received postoperative radiotherapy. Cisplatin-based concurrent chemotherapy was given to 35 % of patients. Oropharynx was the most frequent primary tumor site (60 %). The gross tumor and positive nodes, postoperative surgical bed, and regions of subclinical disease received the median doses of 70.4 Gy, 61.2 Gy, and 50.4 Gy, respectively. Out of the nine regional recurrences, eight were situated ipsilaterally to the grossly involved nodes in levels II and/or III. Two failures occurred under the skull base, corresponding to the lateral retropharyngeal nodes. On the basis of this finding, the department's policy changed (the uppermost level of the CTV was contoured through the base of the skull), so that no recurrence occurred at this level afterwards.

Table 5. Local-regional recurrences following parotid-sparing IMRT

	Patients	Stage III–IV (%)	Failure site T-N-TN	Local-regional recurrences n=49 (12.0 %)		
				In-field	Marginal	Out-field
St. Louis [7]	126	83	4-12-1	10	2	5
San Francisco [30]	150	82	9-2-0	11	0	0
Ann Arbor [11]	133	91	6-9-6	17	4	0
Total	409	85	19-23-7	38 (9.3 %)	6 (1.5 %)	5 (1.2 %)

T – primary tumor, N – lymph nodes, TN – both primary tumor and lymph nodes

Pooled data of the three IMRT studies showed quite high rate of local-regional control, as only 49 of 409 patients (12.0 %) recurred (Tab. 5). In-field recurrences constituted the predominant pattern of failure. Thirty-eight of 49 failures (78 %) occurred at the primary tumor site and/or involved neck nodes. Of note, the UCSF group that reported the lowest incidence of recurrences (7 %) delivered the highest mean doses to the GTV (definitive IMRT 74 Gy, postoperative IMRT 71 Gy). Moreover, the dose per fraction exceeded 2 Gy in the GTV and typically it was 2.12 Gy. The total dose and dose per fraction obviously contributed to the excellent local control but the benefit cannot be quantified. There is a substantial heterogeneity of tumor sites included into these three studies; the median follow-up is still short, ranging from 25 to 32 months, and patients with minimum follow-up of 6 months are also counted; concurrent chemotherapy was administered in 28 % to 71 % of patients.

Low incidence of marginal failures (6/409) is encouraging, if we realize that a significant sparing of the parotid glands was achievable. The mean parotid doses reported by the St. Louis and UCSF groups were 17.7 Gy and 29 Gy, respectively. 82 % of patients treated at the University of Michigan had a mean contralateral parotid dose of 26 Gy or less. Only 5 of 409 patients (1.2 %) experienced recurrence outside the IMRT fields. It is evident that treatment strategy was properly selected and a particular attention has been given to the target volumes definition and delineation.

Recurrent tumors. LU et al from the Sun Yat-Sen University, Guangzhou recently reported on the early results with segmental tomotherapy IMRT (NOMOS Peacock) in the treatment of recurrent nasopharyngeal carcinoma [33]. A dose of 68–70 Gy and 60 Gy was prescribed for the GTV in the nasopharynx and positive neck nodes, respectively. At a median follow-up of 9 months, no patient failed locally.

CLAUS et al treated 14 patients with oropharyngeal and oral cavity carcinoma using IMRT at the Ghent University Hospital, Ghent [9]. Eight patients were re-irradiated for local-regional recurrence with a dose of 50–70 Gy (one patient received 84 Gy including brachytherapy dose). Six of these eight patients (75 %) relapsed in field within four months. Severe late toxicity occurred in one patient who developed the mandible osteoradionecrosis.

Twelve patients with miscellaneous recurrent head and neck cancers (naso-, oro-, and hypopharynx, larynx, paranasal sinus, skin) were treated with IMRT at the University of California Irvine Medical Center, Orange [8]. The prescribed doses ranged from 30 Gy to 70 Gy (more than 50 Gy in 10 patients) in daily fractions of 1.8–2.0 Gy. Six of the eight assessable patients (75 %) showed objective response to radiotherapy. At 4 to 16 months of follow-up, five patients were locally controlled.

Perspectives

The number of IMRT users appears to be growing rapidly. In a recent survey among randomly selected radiation oncologists in the United States, 32 % of respondents stated that they currently used IMRT [38]. Until recently, IMRT was almost exclusively used in academic institutions. At the present time, this advanced technology is rapidly spreading to private and community hospitals.

The existing results are certainly encouraging. In the region of head and neck, several tumor sites are ideally suited for IMRT: skull-base tumors, meningiomas, pharyngeal, laryngeal and oral cavity carcinomas, paranasal sinuses, and thyroid carcinomas. However, no definitive conclusions can be drawn so far. The available data came from reputable academic institutions and it may not be necessarily reproducible in routine clinical practice. Moreover, only short-term results were published with limited numbers of patients. To date, no randomized trials incorporating IMRT have been reported.

Careful definition and delineation of the target volumes is of the utmost importance. Forty-eight radiation oncologists participated in a trial of target volume delineation in cervical esophageal cancer [52]. The study showed up to a sixfold variation in volumes delineated by different physicians. Therefore, it is highly recommended to follow the consensus guidelines for the CT-based delineation of lymph node levels in the neck [20].

One of the most intriguing features of IMRT is the possibility to concurrently deliver different doses of radiation to different target volumes (Fig. 3 and 4). Two accelerated fractionation regimens using IMRT have been proposed. At the Baylor College of Medicine, “simultaneous modulated accelerated radiation therapy” (SMART) boost was initiated [2]. The primary and secondary targets received 60 Gy and 50 Gy in daily fractions of 2.4 Gy and 2.0 Gy. MOHAN et al designed suitable fractionation strategies termed “simultaneous integrated boost” (SIB) [40]. The RTOG trial H-0022 was initiated in 2001 as a phase I-II study of 3D-CRT and IMRT for oropharyngeal cancer. The treatment protocol applies the SIB fractionation strategy. The prescribed dose to the gross

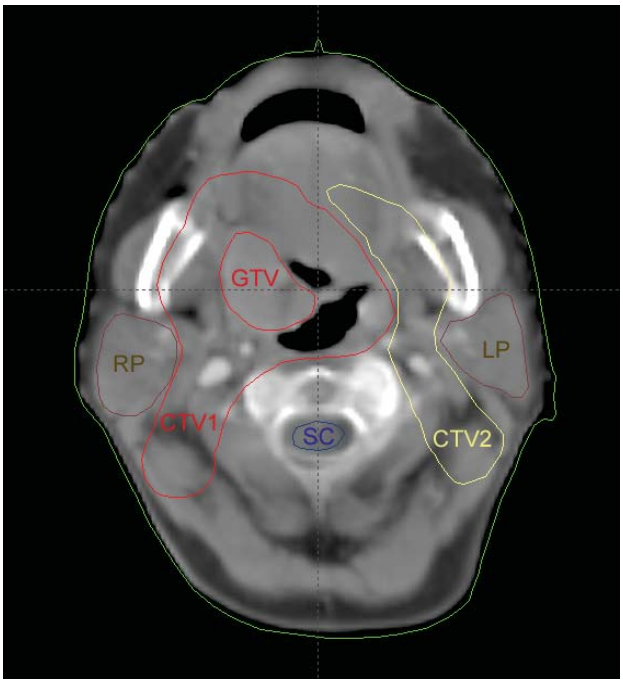

Figure 3. Target volumes and organs at risk (T3 N0 tonsillar carcinoma). GTV – gross tumor volume, CTV1 – clinical target volume 1 (66 Gy), CTV 2 – clinical target volume 2 (60 Gy), RP – right parotid gland, LP – left parotid gland, SC – spinal cord.

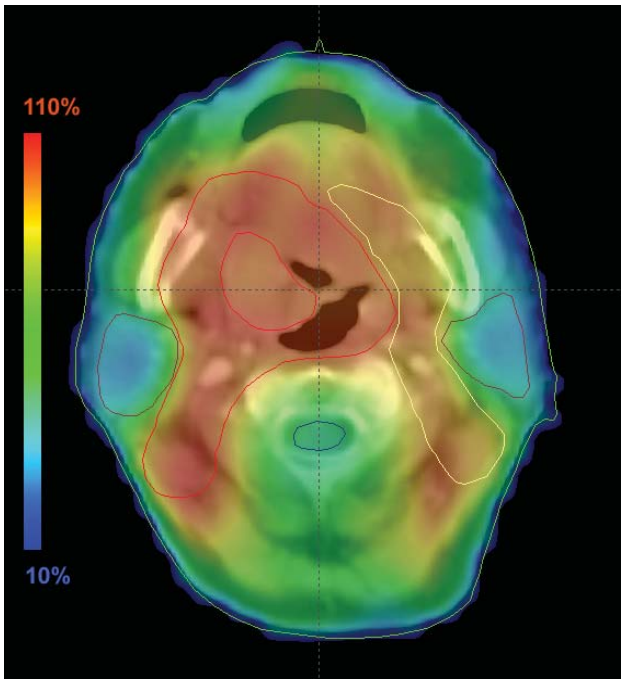

Figure 4. Dose color wash IMRT treatment plan. Different doses in target volumes, sparing of parotid glands and spinal cord (T3 N0 tonsillar carcinoma).

disease is 66 Gy in 30 fractions (2.2 Gy per fraction) and the areas of subclinical disease receive 54 Gy to 60 Gy in 30 fractions (1.8–2.0 Gy per fraction). There are two kinds of benefit associated with the SIB concept. A higher dose per fraction in the GTV may enhance the effect of radiation on hypoxic tumor cells. Moreover, a dose biologically equivalent to 70 Gy at 2 Gy per fraction will be delivered in 6 weeks. The shortening of the overall treatment time is desirable regarding tumor repopulation.

It is time to initiate dose escalation trials in head and neck cancer using IMRT with altered fractionation strategies. Preferably, randomized comparison between IMRT and conventional radiotherapy or chemoradiotherapy should be performed wherever possible.

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