Inoperable oropharyngeal carcinoma treated with concomitant irradiation, mitomycin C and bleomycin – long term results

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Patients with inoperable head and neck tumors were treated concomitantly with radiochemotherapy with mitomycin C and bleomycin in our prospective randomized clinical trial (1991–1993). For the subgroup of patients with oropharyngeal carcinoma the results with radiochemotherapy were significantly superior to irradiation alone. Such scheme of treatment was then adopted as standard method. Here we present the long-term results and dose-response relationships in patients with inoperable oropharyngeal carcinoma treated by the same radiochemotherapy scheme till 1997.

Ninety-five patients with stage III and IV inoperable oropharyngeal squamous cell carcinoma were treated with curative intent, concomitantly with supravoltage irradiation 2 Gy/day 5 times weekly to 60–73 Gy, bleomycin 5 mg 2 times weekly and one application of mitomycin C 15 mg/m^2 after 10 Gy. Logistic dose-response curve was calculated.

Median follow-up was 85 months. The loco-regional control, disease-free survival and overall survival at 5 years were 55 %, 51 % and 32 % (95 % CI: 44–67 %, 41–62 %, 22–42 %), respectively. The probability of new primary malignancy at 5 years was 24 %. In multivariate analysis performance status, biological equivalent dose, dose of bleomycin, and stage were identified as independent prognostic factors for loco-regional control, disease-free, and overall survival. Th γ-value of dose response curve was 2.86.

The outcome of the disease was directly proportional to intensity of irradiation and chemotherapy. It appears that in our concomitant radiochemotherapy MiC increased radioresponsiveness of the tumor by its effect on hypoxic fraction.

Key words: bleomycin, mitomycin, radiochemotherapy, dose-response, oropharyngeal carcinoma

Results of radiation treatment for advanced head and neck carcinoma are unsatisfactory. Chemotherapy as addition to radiotherapy was expected to improve tumor control. While induction chemotherapy did not fulfil these expectations, concomitant administration of irradiation and chemotherapy resulted in increased survival of these patients [32].

To improve poor treatment results in patients with inoperable head and neck tumors, a prospectively designed randomized clinical trial was started in 1991 at the Institute of Oncology and University Department of Otorhinolaryngology in Ljubljana, in which the efficacy of concomitant application of radiotherapy, mitomycin C (MiC) and bleomycin (BLM) was tested against radiotherapy alone. In that study, approved by the National Committee of Ethics, statistically significant improvement of survival was found only in the subgroup of patients with oropharyngeal carcinoma. Therefore, in spite of its rather low statistical power, the trial was prematurely stopped in March 1993 and concomitant radiochemotherapy was adopted at our institutions as standard treatment of inoperable oropharyngeal carcinoma [37, 44].

In the present report, which is an extension of the previously published data, we present the long-term results of the first consecutive 95 patients with inoperable oropharyngeal carcinoma treated with concomitant irradiation, MiC and BLM, some prognostic factors, and the impact of chemotherapy on irradiation dose-response relationship.

Patients and methods

Patients. From March 1991 to December 1997, 419 patients with the oropharyngeal squamous cell carcinoma in advanced stages were referred to The Institute of Oncology and University Department of Otorhinolaryngology in Ljubljana, Slovenia. Sixty-seven of them were fit only for palliation;

246 were treated with curative intent with radiotherapy, because they did not meet the criteria set for the study, and 106 were treated with radiochemotherapy: 11 patients were treated with methotrexate or platinum-based chemotherapy, and 95 patients with inoperable oropharyngeal carcinoma were eligible for our study and were treated by combined simultaneous radiochemotherapy with MiC and BLM. Twenty patients with oropharyngeal carcinoma treated with radiochemotherapy until March 1993, analyzed in previous publications [37, 44], are also included in the present analysis.

Pre-treatment assessment consisted of physical examination, endoscopy of upper aerodigestive tract with biopsy, CT or MRI when necessary, ultrasonographic examination of the neck and abdomen, chest X-ray, complete blood count and electrolytes, prothrombine time, liver and renal function tests. Extent of the disease was determined according to the UICC [38]. Table 1 shows characteristics of the treated patients.

Criteria for inoperability were technical local and/or regional unresecability.

Exclusion criteria for radiochemotherapy with the intent to cure were patients with technically operable tumor, WHO performance status >2, hemoglobin <100 g/l, leukocytes $<3.5x10^9$/l, platelets $<100x10^9$/l, liver enzymes ALT, AST, gamma-GT more than 2 times above normal value and bilirubin, creatinin and prothrombine time above normal values, distant metastases, and synchronous carcinoma elsewhere, except the skin carcinoma.

Table 1. Patient and tumor characteristics

Characteristics	Number
Sex:	
Females	3
Males	92
Age in years	37 – 68 (median 52)
Performance status (WHO)	
0	67
1	26
2	2
Site:	
Anterior wall	21
Lateral wall	65
Posterior wall	2
Superior wall	7
Histological grade:	
I	9
II	63
III	17
Not classified	6
Stage grouping:	
III	21
IVa	62
IVb	12

TN stage:

	N0	N1	N2a	N2b	N2c	N3	Σ
T2	–	–	–	1	–	–	1
T3	12	9	4	13	5	6	49
T4	6	10	2	9	12	6	45
Σ	18	19	6	23	17	12	95

Radiotherapy. Patients were treated with Co-60 or 5 MV supravoltage irradiation, mostly with parallel-opposed fields. The daily dose was 2 Gy applied in one fraction, 5 times per week, specified on the 100 % isodose curve. The primary tumor with additional margin of 1.5–2 cm and regional lymph node areas were within at least 95 % isodose. There was no marked difference in the size of treatment volumes. In order to achieve maximum dose homogeneity (±5 %) inside the treated volume, wedge filters and tissue compensation boluses were used when appropriate. Head-holder with plastic casts and individual shielding blocks were used for all patients. The total dose was aimed to be 66–70 Gy to the primary tumor and clinically evident regional metastases. Clinically uninvolved lymphatic drainage areas of the neck received 50–56 Gy. Posterior neck areas were boosted with 10–12 MeV electrons. The two-stage reduced field technique for clinically evident disease was used: at 40–46 Gy, when spinal cord was shielded, and at 60 Gy, when the irradiated volume had been limited to the residual tumor. If neck metastases were not in the reduced irradiation volume, the boost was applied by electrons with energy and bolus as appropriate. Two-dimensional treatment planning was used in all patients. After simulation and before starting the treatment, and at the field shrinking or at the change of the irradiation technique, verification films were taken at the treatment unit. The lower neck and supraclavicular regions were covered with one anterior field, which abutted the primary upper neck fields at the skin surface. The dose was specified at the depth of 2 cm.

On the day of the application of MiC, patients were irradiated twice with the interfraction interval of 6 hours.

Quality assurance and quality control. Dosimetry checks were performed once weekly on regular basis with water or "plastic water" phantom, electrometer, and Farmer type cylindrical ionization chamber for high energy photons, and with planparallel ionization chamber for electrons, following International Agency for Atomic Energy TRS-398 dosimetry protocol. Isocenter accuracy, field dimension, and security interlocks were checked every day, while other mechanical checks were performed on monthly basis.

Biological dose. Biologically effective dose (BED) was calculated according to the formula: $BED = TD \times (1 + d/\alpha/\beta) - K \times (T_t - T_d)$, where TD = total tumor dose in Gy, T_t = total treatment time in days, K = daily dose equivalent of repopulation in units of $Gy_{a/b}\,day^{-1}$ (K = 0.6, and $\alpha/\beta = 10$), and T_d = lag time in days to the onset of effective repopulation during the treatment. It was assumed that $T_d = 28$ days [16, 43].

Chemotherapy. The planned chemotherapy regimen consisted of intramuscular applications of BLM 5 mg twice a week during radiotherapy. After 10 Gy of irradiation, MiC 15 mg/m^2 was applied intravenously as reported elsewhere [37, 44].

Follow-up. During the treatment, loco-regional and systemic treatment-related toxicity was monitored weekly. In the first year after completion of the therapy, the patients were followed once a month, and after that, the interval was prolonged for a month in each successive year until the sixth year when the patients were examined once each year. At each follow-up visit, we looked for possible progression of the disease, late adverse effects on the healthy tissues and possible new primary malignancies. Clinical examination, complete blood count, electrolytes, liver and renal function tests were routinely performed at each follow up. Chest X-ray was checked every year. Acute and chronic toxicity were defined according to National Cancer Institute Common Toxicity Criteria [10].

Endpoints. The primary end-point was loco-regional control after radiotherapy. The definition of this end-point was complete and persistent disappearance of the primary tumor (T-site) and the disease in regional lymph nodes (N-site) after radiotherapy. The evaluation was performed clinically and supplemented with endoscopy and/or biopsy in case of doubt. Failure was recorded in the event of a recurrent tumor, or if the primary tumor never completely disappeared. In the latter situation it was assumed that the treatment had failed at its end.

Secondary end-points included disease-free survival, overall survival and treatment-related morbidity. For the disease-free survival, the event was loco-regional recurrence or distant metastases, and for overall survival, the event was any death, irrespective of cause. All time estimates were performed using the date of the beginning of treatment as the initial value.

Statistical methods. The actuarial values of the end-points were evaluated by the KAPLAN-MEIER product-limit analysis [22] and the logrank test was used to test the difference between groups. COX [12] regression model was used to define independent prognostic factors. In the multivariate model prognostic factors that were found to be significant in the univariate analysis were included as binary variables. The statistical significance of hemoglobin drop during the treatment period was tested with paired t-test [2]. All reported p-values were two-sided and considered statistically significant at $p \geq 0.05$.

To define the cut points, the values of total tumor dose, BED, the dose of MiC and BLM were sorted by size and divided in 5–6 categories. For each category, the Kaplan-Meier survival curve was calculated. We found that the survival increased proportionally with the increasing dose. The dose, where the difference in loco-regional control or survival at 5 years was the largest, was taken as the cut point.

Dose response curve was constructed using logistic model. Statistics were calculated with SPSS 10.0 and SigmaPlot 6.0 (SPSS Inc. USA).

Results

Compliance. The median total irradiation dose was 68 Gy (60–73 Gy), median treatment time was 48 days (40–78 days), BED 69 Gy_{10} (49–75.6 Gy_{10}), median dose of MiC 14.7 mg/m^2 (7.6–16.5 mg/m^2, when the liver enzymes were above normal value the dose of MiC was reduced) and BLM 25 mg (range 5–75 mg the dose was reduced due to mucositis and/or oral infection). Three patients refused the application of MiC, and three refused BLM. In case of severe mucositis, the treatment was interrupted, and /or BLM was stopped, or the treatment was ended before planned irradiation tumor dose was achieved.

Treatment outcome. Median follow up was 85 months (range 46–146 months). At the time of analysis, 70/95 patients were dead: 42 of oropharyngeal carcinoma, 16 of second primary without evidence of progression, and 12 of other causes. Twenty-five patients were alive without disease.

Sixty-seven patients had the WHO performance status 0, and 28 patients 1 or 2. There was no statistically significant difference in distribution of performance status between compared groups.

The probability of loco-regional control, disease-free survival and overall survival at 5 years was 55 % (95 % CI=44–67 %), 51 % (95 % CI=41–62 %), and 32 % (95 % CI=22–42 %), respectively (Fig. 1). Median overall survival was 27 months.

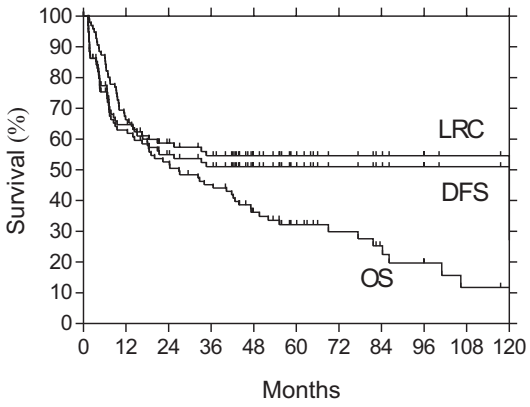

Figure 1. Loco-regional control, disease free survival, and overall survival of 95 treated patients. LRC – loco-regional control, DFS – disease free survival, OS – overall survival.

The probability of primary tumor control was for T3 and T4 73 % (95 % CI=60–86 %), and 52 % (95 % CI=37–67 %), respectively (p=0.022). The probability of regional control for N0, N1-N2c, and N3 lymph-node metastases was 94 % (88–100 %), 81 % (71–91 %), 13 % (0–37 %), respectively (p=0.0001).

Local recurrences, regional recurrences and distant

metastases developed within the first year after the beginning of the treatment in 30/32 (94 %), 16/20 (75 %) and 8/12 (67 %), respectively.

In univariate analysis, the performance status, stage of disease, total tumor dose, BED, the total dose of BLM and MiC influenced the outcome of the treatment. Table 2 shows the influence of established prognostic factors on LRC, DFS, and OS as obtained by univariate analysis.

The multivariate analysis showed that the performance status, stage, BED, dose of BLM, remained statistically significant independent prognostic factors for loco-regional control, disease-free survival and overall survival, while MiC had statistically significant influence only on DFS and OS (Tab. 3).

The intensity of treatment showed marked effect on the treatment outcome (Fig. 2).

Table 2. Impact of some prognostic factors on outcome - univariate analysis

		Loco-regional control at 5 years		Disease-free survival at 5 years		Overall survival at 5 years	
	n	(%)	p	(%)	p	(%)	p
All patients	95	55	–	51	–	33	–
Performance							
0	67	66		63		45	
1, 2	28	25[1]	0.0001	20[1]	0.0001	0	0.001
T- stage[2]							
T3	49	62		59		37	
T4	45	46	0.042	41	0.038	28	0.21
N-Stage							
N0	18	70		70		36	
N1-2c	65	59	0.009	57	0.0008	39	0.002
N3	12	0		0		0	
Stage grouping							
III	21	75		75		46	
IVa	62	57	0.005	54	0.0004	36	0.001
IVb	12	0		0		0	
Tumor dose							
≥68Gy	56	64		61		44	
<68 Gy	39	40	0.029	37	0.023	19	0.037
BED							
≥65 Gy_{10}	75	63		59		38	
<65 Gy_{10}	20	21	0.0003	18	0.0002	15	0.022
Dose of BLM							
≥35 mg	32	70		64		30	
<35 mg	63	46	0.029	44	0.047	9	0.037
Dose of MiC							
≥14.1 mg/m^2	76	57		56		33	
<14.1 mg/m^2	19	41	0.23	9	0.032	0	0.017
Dose of both drugs							
High dose	25	83		79		50	
Low dose	70	44	0.002	41	0.002	6	0.013

n – number of patients; BED – biologically effective dose; BLM – bleomycin; MiC – mitomycin C, High dose – MiC ≥ 14.1 mg/m^2 + BLM ≥ 35 mg; Low dose – MiC ≥ 14.1 mg/m^2 + BLM < 35 mg or MiC ≥ 14.1 mg/m^2 + BLM < 35 mg or MiC < 14.1 mg/m^2 + BLM ≥ 35 mg. [1] last censored at 59 months; [2] tumor T2 not counted.

Table 3. Multivariate analysis of prognostic factors

	Loco-regional control			Disease-free survival			Overall survival		
	Hazard ratio	95 % CI		Hazard ratio	95 % CI		Hazard ratio	95 % CI	
		Lower	Upper		Lower	Upper		Lower	Upper
STAGE (III & IVa vs.IVb)	1.478	1.013	2.159	1.615	1.137	2.294	1.566	1.114	2.199
PERFORMANCE (0 vs. & 1,2)	3.380	1.676	6.819	3.116	1.600	6.069	3.994	2.227	7.165
BED (≥65 Gy_{10} vs. <65 Gy_{10})	3.262	1.611	6.608	3.248	1.653	6.381	1.735	0.969	3.104
BLEOMYCIN (≥35 mg vs. <35 mg)	2.569	1.156	5.710	2.356	1.133	4.896	1.819	1.060	3.122
MITOMYCIN C (≥14.1 mg/m^2 vs. <14.1 mg/m^2)	1.800	0.831	3.901	2.352	1.174	4.709	2.335	1.338	4.073

CI – confidence interval; BED – biological equivalent dose

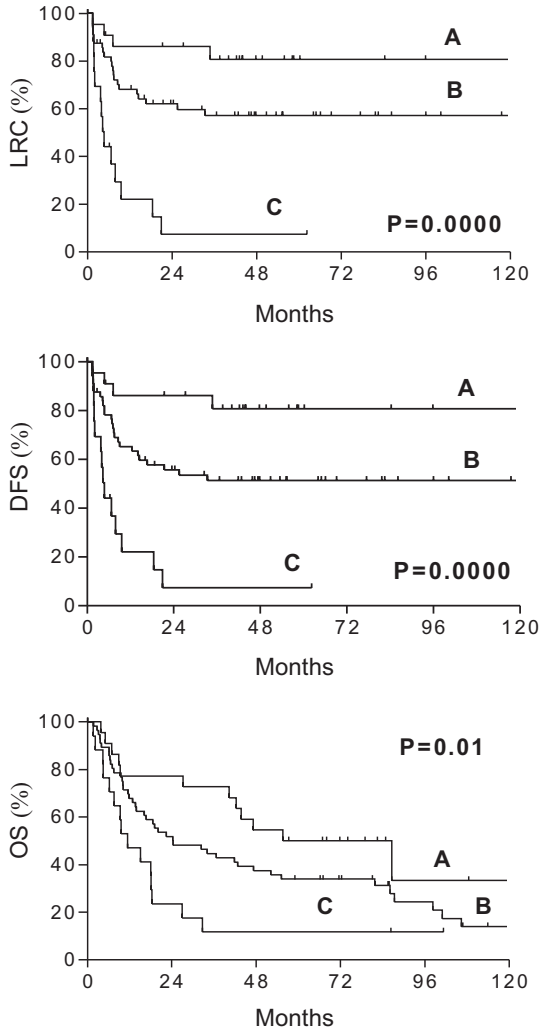

Figure 2. Survival according to the intensity of treatment. A – high dose chemotherapy (mitomycin C ≥14.1 mg/m^2 + bleomycin ≥35 mg) + high biologically equivalent dose (≥65Gy$_{10}$), n=22.
B – either the dose of chemotherapy high or biologically equivalent dose was high, n=56.
C – low chemotherapy (mitomycin C <14.1 mg/m^2 + bleomycin <35 mg) + low biologically equivalent dose (<65 Gy$_{10}$), n=17.

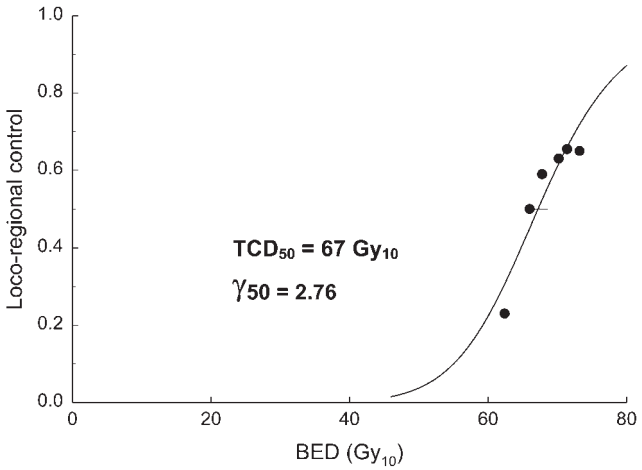

Figure 3. Logit dose-response curve for probability of loco-regional control for 95 patients treated with concomitant radiochemotherapy. 95 % confidence interval at 50 % of loco-regional control = 66.0–68.4 Gy$_{10}$ is shown. BED – biologically effective dose, TCD50 – 50 % tumoricidal dose, γ_{50} – steepnes of the irradiation dose-response curve.

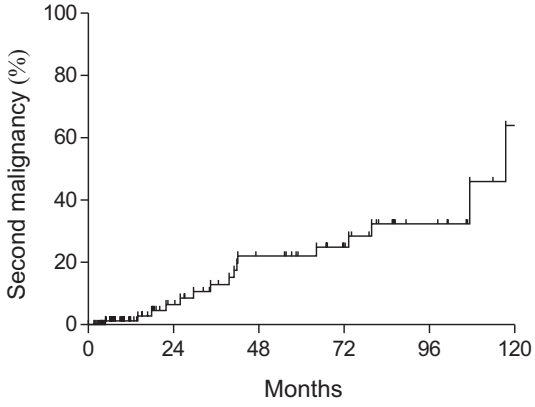

Figure 4. The probability of second malignancy.

The loco-regional tumor control was very much BED dependent. The 50 % loco-regional tumor control probability was 67 Gy$_{10}$ and the γ_{50} value of the dose-response curve was 2.76 (Fig. 3).

Anatomical site, histological grade and age did not influence significantly either loco-regional control or survival of patients. Patients with hemoglobin level Hb≥140 g/l had better loco-regional control (61 %), as patients with Hb<140 g/l (51 %) but the difference was not statistically significant.

Distant metastases. Distant metastases were diagnosed in 14 patients, 5 of them developed in 12 patients with IVb stage of disease. Bones were affected in 8, lungs in 6, and other organs in 7 patients; among them, 6 with local, 1 with regional, 3 with local and regional recurrence, and 4 without loco-regional disease.

Second primary. There were diagnosed altogether 18 metachronous new primaries in 17 patients (18 %): 9 in the lungs, 3 in the oesophagus, 2 in the tongue, and one in hypopharynx, stomach rectum and kidney pelvis. The probability of developing a new primary at 5 years was 24 % (95 % CI=12–36 %) (Fig. 4). Three of 17 patients were cured: one carcinoma of the tongue, one of the rectum and one of the lungs.

Acute toxic effects. The most prominent acute toxic effect was mucositis. Grade 3 mucositis was present in 59/95 (62 %) patients, and grade 3 dermatitis in 16/95 (17 %) patients. Tube feeding was introduced in 4 patients.

Mean hemoglobin value in the treated patients dropped from 140 g/l before the treatment to 120 g/l at the end of treatment ($p<0.0001$). Grades of leukopenia and thrombopenia at their nadir values are shown in Table 4.

Table 4. Leukopenia and thrombopenia in 95 treated patients

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	33	22	29	10	1
Thrombopenia	66	16	8	5	0

One patient died during the treatment because of septicaemia, associated with grade 2 leukopenia.

The median weight loss during the treatment was 10 % (range 0–22 %). It had negative impact on survival, but not statistically significant.

Late toxic effects. Most patients suffered of xerostomia and dental caries of grade 2 or less. Grade 3 toxicity developed in 11 patients: 5 patients developed fibrosis (in one patients associated with moderate edema, and in one with nerve palsy), 1 xerostomia, 1 teleangiectasia, 4 trismus associated with limited self-healing bared mandible in one. Grade 4 developed in 2 patients: both had severe necrosis of the mandible, one demanding surgery. The probability of developing toxicity grade ≥3 was 13 % at two years after completion of the treatment and 26 % at 48 months and remained at the same level thereafter (Fig. 5). No pulmonary toxicity associated with BLM was registered.

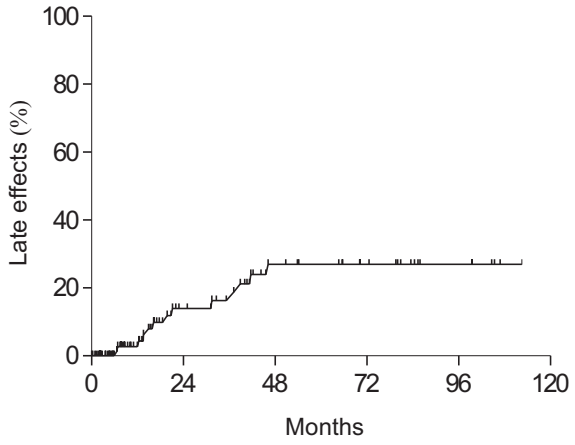

Figure 5. Probability of late effects.

Discussion

The present analysis confirms the optimism we gained by the results for advanced inoperable oropharyngeal carcinoma in small randomized trial performed at our institutions between 1991–1993 [37, 44]. The 5-year loco-regional control of 56 %, disease-free survival of 51 % and overall survival of 32 % justify the choice of the treatment regimen we made, and compare favorably to the results reported in the literature.

There are numerous reports on concomitant treatment with irradiation and chemotherapy in advanced head and neck carcinoma [e.g. 1, 20, 21, 26, 39]. In majority of them, various tumor sites, each with different prognosis, are included in the study and the results are reported for all sites together. The reports dealing only with concomitant radiochemotherapy for advanced oropharyngeal squamous cell carcinoma are scarce (Tab. 5) [5, 8, 9, 15, 27]. Even in these studies the extent of disease varies considerably. Two authors [5, 15] included in their studies also stage II disease. In one study only [39], it is stated that exclusively inoperable cases were included. In our series, all tumors were technically inoperable, which means that radical resection, either regional and/or local, was not possible even with the primary microvascular free flap reconstruction. Namely, at our institutions, the standard approach for the patients with advanced oropharyngeal carcinoma is, whenever feasible, primary operation followed by radiotherapy.

In four series that included only the patients with oropharyngeal carcinoma (Tab. 5) [5, 8, 9, 27, 39], the tested cytotoxic drugs were cisplatin (or carboplatin) and 5-FU. MiC, given as a single injection on the first day of radiotherapy, was added to this combination in one study [5]. The monochemotherapy with BLM was tested in one study only [15]. In the present series, BLM was used due to its radiosensitizing effect on oxygenated tumor cells [40, 17, 15, 3], while MiC, a bioreductive alkylating agent was chosen because of its selective toxic effect on radioresistant hypoxic tumor cells [19, 23]. In our study, the 5-year loco-regional control was comparable to that reported by CALAIS et al [8, 9], and at 2 years, it was lower than in the study of BERGER et al [5] but comparable to the results obtained by STAAR et al [39]. Regarding the disease-free survival, our results are somewhat better than those of other reports, while the overall survival was comparable to others (Tab. 5). It seems that in patients with advanced oropharyngeal carcinoma, the mode of chemotherapy (induction chemotherapy vs. concomitant) is more important than the choice of the drugs. It seems that hyperfractionated accelerated irradiation with concomitant chemotherapy is not better than conventional radiochemotherapy [39].

The treatment intensity is important for disease control and survival (Fig. 2). Therefore, it does not seem recommendable to interrupt the treatment, or to end it prematurely or to stop BLM, when mucositis becomes severe. Probably, if tube

Table 5. Oropharyngeal carcinoma – results of concomitant radiochemotherapy

Author (reference)	n	Treatment	Gy	Follow up (Years)	LRC (%)	DFS (%)	OS (%)	Acute toxicity grade ≥3	Late toxicity grade ≥3	Remarks
Eschwege et al. (15)	107	Conventional RT + BLM (15 mg 2 x weekly up to 150 mg)	70	5	-	22	22	Mucositis 68% Dermatitis 24% Pneumonitis 2%	-	All tumors >2 cm, regardless of the nodal status
				10	-	-	<10			
Berger et al. (5)	27	Conventional RT + Cisplatin (20 mg/m^2 days 1-4) + 5-FU (400 mg/m^2 days 1-4) + MiC (10 mg/m^2 day 1)	70	2	80	31	48	Mucositis (81%) Mean weight loss 9.6% Neutropenia 30% Anemia 15% Thrombocytopenia 41% 3 toxic deaths	-	Stages II - IV.
Calais et al. (8, 9)	109	Conventional RT Carboplatin (70 mg/m^2 days 1-4) + 5-FU (600mg/m^2 days 1-4) 3 cycles	70	5	53	30	-	Mucositis 67% Dermatitis 21% Leukopenia 4% Thrombopenia 6% 1 toxic death >10% weight loss 13%	Xerostomia 9% Severe fibrosis 11%	Stages III and IV
Staar et al. (39)	87	IHFA RT Carboplatin (70mg/ m^2 days 1-5 and 29-33)+ 5-FU (600mg/m^2 days 1-5 and 29-33)	69.9	2	53	-	-	Mucositis 68% Dermatitis 30% Leukopenia 18% Thrombopenia 5%	Osteoradionecrosis 5.8% Dependence on tube feeding 30% of survivors ≥ years	Inoperable stages III and IV
Olmi et al. (27)	64	Conventional RT+ Carboplatin (75mg/m^2 days 1-4) + 5-FU (1000 mg/m^2 days 1-4) 3 cycles	66 – 70	2	-	42	51	Mucositis 48 % Dermatitis 16% Leukopenia 23% Thrombopenia 4.5% Anemia 2% Nephrotoxicity 2%	Skin 2.5% Subcutis 2.7% Mucosa 5.1%	Excluded stages T1N1 and T2N1
Present study	95	Conventional RT MiC (15 mg/m^2 day 5) + BLM (5 mg 2 x weekly)	68 (median)	2	60	55	52	Mucositis 62% Dermatitis 17% Leukopenia 12% Thrombopenia 5%	Edema 2% Fibrosis 6% Mandibular necrosis 4% Positive Lhermitte sign 1%	Inoperable stages III and IV
				5	56	51	34	Mean hemoglobin drop 14 % Median weight loss 10% 1 toxic death No pneumonitis		

n – number of patients with radiochemotherapy per study, LRC – loco-regional control, DFS – disease free survival, OS – overall survival, RT – radiotherapy, BLM – bleomycin, 5-FU – 5-fluorouracyl, MiC – mitomycin C, IHFA – intensified hyperfractionated accelerated.

feeding or jejunal feeding had been used more frequently, more patients could be treated with higher irradiation dose and dose of cytostatic drugs.

However, the price for improved survival was rather severe acute toxicity, the main being mucosits attributed mainly to the sensitising effect of BLM. Nevertheless, in view of improved treatment results and late toxicity within acceptable limits, this seems to be acceptable treatment.

The decision on the intensity of treatment in patients with stage IVb disease is more problematic. All but one of 12 N3-patients in our series died of cancer, and their survival was short (median 10 months). Five of them developed distant metastases. Therefore, one should be aware of limited curative potential of radiochemotherapy and be cautious when planning therapy in order to avoid too much morbidity. These patients are at greater risk to develop distant metastases than the patients with less advanced disease.

The steepness of radiation dose-response curves of oropharyngeal carcinoma is usually shallow, with gamma values (γ_{37} or γ_{50}) ranging from 0.5 to 1.6 [4, 31, 41] (Tab. 6). This means 0.5–1.6 % increase of local control per 1 % increase of the total tumor dose at the steepest part of the curve. The reason for shallowness is heterogeneity in various tumor characteristics, such as tumor size, its radiosensitivity and size of hypoxic fraction. Treatment characteristics, as inhomogeneities of irradiation dose have further flattening effect.

Table 6. Steepness (γ) of the clinical dose-response curve for carcinoma of the oropharynx

Tumor site	γ_{37}	γ_{50}	Reference
Oropharynx	1.6	–	Bentzen et al. 1991 (4)
Tonsil T1-4	–	1.29	Perez et al.1982 (31)
Neck nodes N1-3	–	1.03	
Base of tongue			
T1-2	0.9	–	Thames et al. 1980 (41)
T3-4	0.5		
Oropharynx (Stage III an IV)			
Loco-regional control	–	2.76	Present study

γ_{37}, γ_{50} the steepest part of the Poisson and logistic dose-response curve.

The dose-response curve calculated from our data is steeper than usually obtained for oropharyngeal carcinoma (Tab. 6, Fig. 3). The explanation might be as follows. The hypoxic fraction of the tumor cells is the most radioresistant fraction in the tumor. The MiC kills hypoxic tumor cells and/or renders them more radioresponsive [19, 23]. The whole population of clonogenic tumor cells becomes less heterogeneous in terms of radioresponsivness, which increases the steepness of the dose-response curve. Thus, the tumor cure becomes much more dose dependent: 2 Gy_{10} difference at the total biological tumor dose 67 Gy_{10}, which is in our case TCP 50, means 8.2 % change in tumor response. BLM, a radiomimetic cytotoxic agent, increases radiosensitivity of the oxic fraction of the tumor [40]. However, from the present study it is difficult to infer whether BLM also played a role in making the dose-response curve steeper.

The efficacy of radiation therapy in patients with squamous cell carcinoma of the head and neck has been found to correlate with the haemoglobin concentration in several studies (reviewed by OVERGAARD [29]). In our study, LRC in patients with low hemoglobin was 51 %, and in those with high hemoglobin 61 %, which was not statistically significant. The ratio in LRC-rate between low and high hemoglobin group was thus 0.84. The ratios in LRC-rates between low and high hemoglobin as we calculated from published data for head and neck carcinoma [7, 13, 18, 24, 25, 28, 33, 34] ranged from 0.55–0.93. In the two studies using MiC in the treatment scheme [7, 18], the rates were similar to ours: 0.82 and 0.93, while in the others the ratio was generally much lower. It seems that the negative effect of low hemoglobin level was masked by radiosensitizing and cytotoxic effect of MiC upon the hypoxic fraction, reducing it considerably and thus rendering the tumor response less dependent on hemoglobin concentration. The reason for statistically negative effect of hemoglobin could also be attributed to the small number of patients.

For patients with carcinomas of the head and neck, the rates of second carcinoma range from 8–25 % [6, 11, 14, 30, 35, 36]. The incidence of secondary malignancies in our group of patients – 18 % – falls in this range. The second carcinomas considerably lowered the long term overall survival, because only 3 of 17 patients could be cured: one carcinoma of the tongue, one of the rectum and one of the lungs. Therefore, rigorous follow-up is indicated after the treatment of the initial cancer to detect the second malignancies in curable stage.

Conclusions

In our study, the treatment results in terms of tumor control and toxicity for advanced inoperable oropharyngeal carcinoma as achieved with concomitant conventional irradiation and chemotherapy with MiC and BLM are comparable to the results reported with platinum based radiochemotherapy. The outcome of the disease was dependent on intensity of chemotherapy and irradiation. The dose of chemotherapy, BED, performance status and stage are independent prognostic factors for loco-regional control, disease-free survival, and overall survival. We believe that in our concomitant radiochemotherapy MiC increased radioresponsiveness of the tumor by its effect on hypoxic fraction.

References

[1] ADELSTEIN DJ, SAXTON JP, LAVERTU P, TUASON L, WOOD BG et al. A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone with

resectable stage III and IV squamous cell head and neck cancer: Preliminary results. Head Neck 1997; 19: 567–575.

[2] ARMITAGE P. Statistical methods in medical research. Oxford: Blackwell Scientific, 1971.

[3] AUERSPERG M, ŠOBA E, VRASPIR-PORENTA O. Intravenous chemotherapy with synchronization in advanced cancer of oral cavity and oropharynx. Z Krebsforsch 1977; 90: 149–159.

[4] BENTZEN SM, JOHANSEN LV, OVERGAARD J, THAMES HD. Clinical radiobiology of squamous cell carcinoma of the oropharynx. Int J Radiat Oncol Biol Phys 1991; 20: 1197–1206.

[5] BERGER C, CHAPET S, REYNAUD-BOUGNOUX A, GARAND G, LE FLOCH O et al. Enhanced acute toxicity in oropharynx carcinoma treated with radiotherapy and concomitant cisplatin, 5-fluorouracil and mitomycin C. Eur J Cancer 1996; 32: 1707–1711.

[6] BLACK RJ, GLUCKMAN IL, SHUMRICK DA. Multiple primary tumours of the upper aerodigestive tract. Clin Otolaryngol 1983; 8: 277–281.

[7] BUDACH VG, GEISMAR D, HAAKE K, STUSCHKE M, BAUMANN M et al. Hemoglobin is an independent prognostic factor in locally advanced head & neck cancer – three year results from a German multicentre trial (ARO 95/6). Int J Radiat Oncol Biol Phys 2001; 51 Suppl 1: 183–184.

[8] CALAIS G, ALFONSI M, BARDET E, SIRE C, GERMAIN T et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-staged oropharynx carcinoma. J Natl Cancer Inst 1999; 91: 2081–2086.

[9] CALAIS G, ALFONSI M, BARDET E, SIRE C, GERMAIN T et al. Radiation alone (RT) versus RT with concomitant chemotherapy (CT) in stages III and IV oropharynx carcinoma. Final results oft he 94-01 GORTEC randomized study. Int J Radiat Oncol Biol Phys 2001; 51 Suppl 1: 1–2.

[10] Common Toxicity Criteria Version 2.0. National Cancer Institute 1999.

[11] COOPER JS, PAJAK TF, RUBIN P, TUPCHONG L, BRADY LW et al. Second malignancy in patients who have head and neck cancer: Incidence, effect on survival and implicantions based on RTOG experience. Int J Radiat Oncol Biol Phys 1989; 17: 449–456.

[12] COX DR. Regression models and life-tables. J Royal Stat Soc 1972; 34: 187–220.

[13] DALY T, PAULSEN MG, DENHAM JW, PETERS LJ, LAMB DS et al. The effect of anaemia on efficacy and normal tissue toxicity following radiotherapy for locally advanced squamous cell carcinoma of the head and neck. Radiother Oncol 2003; 68: 113–122.

[14] ERKAL HS, MENDENHALL WM, AMDUR RJ, VILLARET DB, STRINGER SP. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. J Clin Oncol 2001; 19: 1358–1362.

[15] ESCHWEGE F, SANCHO-GARNIER H, GERARD JP. Ten-year results of randomized trial comparing radiotherapy and concomitant bleomycin to radiotherapy alone in epidermoidal carcinoma of the oropharynx: Experience of the European Organization for Resarch and Treatment of Cancer. Natl Cancer Inst Monogr 1988; 6: 275–278.

[16] FOWLER JF. The linear quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1998; 62: 679–694.

[17] FU KK, PHILLIPS TL, SILVERBERG IJ, JACOBS C, GEOFFINET DR et al. Combined radiotherapy and chemotherapy with bleomycin and methotrexate for advanced inoperable head and neck cancer: Update of Northern California Oncology Group randomized trial. J Clin Oncol 1987; 5: 1410–1418.

[18] GLASER CM, MILLESI W, KORNEK GV, LANG S, SCHÜLL B et al. Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharynx. Int J Radiat Oncol Biol Phys 2001; 50: 705–715.

[19] GRAU C AND OVERGAARD J. Radiosensitizing and cytotoxic properties of mitomycin C in a CH3 mouse mammary carcinoma *in vivo*. Int J Radiat Oncol Biol Phys 1991; 20: 265–269.

[20] GRAU C, PRAKASH JA, JABEEN K, KHAN AR, ABEYAKOON S et al. Radiotherapy with or without mitomycin C in the treatment of locally advanced head and neck cancer: results of the IAEA multicenter randomized trial. Radiother Oncol 2003; 67: 17–26.

[21] HADDAD E, MAZERON JJ, MARTIN M, VERGNES L, BRUN B et al. Comparison of concomitant radiotherapy and chemotherapy with radiotherapy alone in cancers of the head and neck: Results of the randomized trial. Bull Cancer Radiother 1996; 83: 97–103.

[22] KAPLAN EL, MEIER P. Nonparametric estimation from incomplete observations. JASA 1958; 53: 457–481.

[23] KENNEDY KA, ROCKWELL S, SARTORELLI AC. Preferential activation of mitomycin C to cytotoxic metabolites by hypoxic tumour cells. Cancer Res 1980; 40: 2356–2360.

[24] MC GEE KP, FEIN DA, LEE WR, HANLON AL, RIDGE JA et al. Pretreatment hemoglobin level influences local control and survival of T1-T2 squamous cell carcinomas of the glottic larynx. Int J Radiat Oncol Biol Phys 1995; 32: 161.

[25] LEE RW, BERKEY B, MARCIAL V, FU KK, COOPER JS et al. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. Int J Radiat Oncol Biol Phys 1998; 42: 1069–1075.

[26] MERLANO M, VITALE V, ROSSO R, BENASSO M, CORVO R et al. Treatment of advanced squamous-cell carcinoma of the head and neck. N Engl J Med 1992; 327: 1115–1121.

[27] OLMI P, CRISPINO S, FALLAI C, TORRI V, ROSSI F et al. Locoregionally advanced carcinoma of the oropharynx: Conventional radiotherapy vs. Accelerated hyperfractionated radiotherapy vs concomitant radiotherapy and chemotherapy – a multicenter randomized trial. Int J Radiat Oncol Biol Phys 2003; 55: 78–92.

[28] OVERGAARD J, HANSEN HS, ANDERSEN AP, HJELM-HANSEN M, JORGENSEN K et al. Misonidazole combined with split-course radiotherapy in the treatment of invasive carcinoma of larynx and pharynx: report from the DAHANCA 2 study. Int J Radiat Oncol Biol Phys 1989; 16: 1065–1068.

[29] OVERGARD J. Sensititation of hypoxic tumour cells – clinical experience. Int J Radiat Oncol Biol Phys 1989; 56: 801–811.

[30] PARKER RD, ENDSTROM JE. Second primary cancers of the

head and neck following treatment of initial primary head and neck cancers. Int J Radiat Oncol Biol Phys 1988; 14: 561–564.

[31] PEREZ CA, PURDY JA, BREAUX SR, OGURA JH, VON ESSEN S. A nonrandomized comparison of preoperative radiation and surgery or radiation alone: Long-term results. Cancer 1982; 50: 2314–2322.

[32] PIGNON JP, BOURHIS J, DOMENGE C, DESIGNE L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three metaanalyses of updated individual data. MACH-NC Collaborative Group. Lancet 2000; 355: 949–955.

[33] PROSNITZ RG, YAO B, FARRELL CL, CLOUGH R, BRIZEL DM. Pretreatment hemoglobin levels are correlated with the effectiveness of radiation and concurrent chemotherapy in advanced head and neck cancer. Int J Radiat Oncol Biol Phys 2002; 54 Suppl 1: 73.

[34] RUDAT V, DIETZ A, SCHRAMM O, CONRADT C, MAIER H et al. Prognostic impact of total tumor volume and hemoglobin concentration on the outcome of patients with advanced head and neck cancer after concomitant boost radiochemotherapy. Radiother Oncol 1999; 53: 119–125.

[35] SCHWARTZ LH, OZSAHIN M, ZHANG GN, TOUBOUL E, DE VATAIRE F et al. Synchronous and metachronous head and neck carcinomas. Cancer 1994; 74: 1933–1938.

[36] SHONS AR, McQUARRIE DG. Multiple primary epidermoid carcinoma of the upper aerodigestive tract. Arch Surg 1985; 120: 1007–1009.

[37] SMID L, LESNICAR H, ZAKOTNIK B, SOBA E, BUDIHNA M et al. Radiotherapy, combined with simultaneus chemotherapy with Mitomycin C and Bleomycin for inoperable head and neck cancer – Preliminary report. Int J Radiat Oncol Biol Phys 1995; 32: 769–775.

[38] SOBIN LH, WITTEKIND C. TNM classification of malignant tumours. 5th Edition. New York: Wiley, 1997.

[39] STAAR S, RUDAT V, STUETZER H, DIETZ A, VOLLING E et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy – results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001; 50: 1161–1171.

[40] TEICHER BA, LAZO JS, SARTORELLI AC. Classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic tumor cells. Cancer Res 1981; 41: 73–81.

[41] THAMES HD, PETERS LJ, SPANOS W, FLETCHER GH. Dose response of squamous cell carcinomas of the upper respiratory and digestive tracts. Br J Cancer 1980; 41 Suppl IV: 35–38.

[42] VERMUND H, KAALHUS O, WINTHER K, TRAUSJO J, THORUD E et al. Bleomycin and radiation therapy for squamous cell carcinoma of the upper aero-digestive tract. Int J Radiat Oncol Biol Phys 1985; 11: 1877–1886.

[43] WITHERS HR, PETERS LJ, TAYLOR JM, OWEN JB, MORRISON WH et al. Local control of carcinoma ofthe tonsil by radiation therapy: an analysis of of paterns of fractionation in nine institutions. Int J Radiat Oncol Biol Phys 1995; 33: 549–562.

[44] ZAKOTNIK B, ŠMID L, BUDIHNA M, LESNICAR H, SOBA E et al. Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. Int J Radiat Oncol Biol Phys 1998; 41: 1121–1127.